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Measurement of urinary kidney injury molecule -1 level as an early biomarker of renal impairment in overweight/obese children and adolescents with nonalcoholic fatty liver disease

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Abstract: **Background:** The prevalence and extra hepatic complications of nonalcoholic fatty liver disease (NAFLD) in children have increased dramatically over the past decade. **Objectives:** to determine early renal functional alterations in overweight / obese children and adolescents with NAFLD by measuring urinary kidney injury molecule-1 (uKIM-1) level, and to evaluate its relation to the degree and various clinico-laboratory parameters of NAFLD. **Subjects and Methods:** In this case–control study, urinary KIM-1 was measured in 60 obese/overweight children and adolescents, 30 of them with NAFLD proved by ultrasound (group I), 30 without NAFLD (group II), and compared with 20 healthy children of the same age and sex (controls). Clinical examination included anthropometric measurements. Laboratory investigations including liver function, lipid profile, kidney function, urine albumin, serum glucose, insulin and urinary KIM-1 level. **Results:** Significant increase in body mass index (BMI), waist and hip circumferences, waist to hip ratio (W/HR), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total cholesterol, low-density lipoprotein, triglycerides, fasting serum insulin, insulin resistance (IR) in obese subjects compared to controls. Urinary KIM-1 showed no significant difference between the studied groups but correlated with the degree of hepatic steatosis. Urinary KIM-1 levels correlated significantly with W/H ratio, Alp, triglycrides and IR. Urinary albumin levels showed no significant difference between the groups. **Conclusion:** Urinary KIM-1 can be used as a biomarker for early detection of renal affection in NAFLD children and is promising but further studies are needed to confirm this result.
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Keywords: Measurement; urinary; kidney; injury; molecule; biomarker; renal impairment; children; adolescents; nonalcoholic; fatty; liver; disease

1. Introduction

Nonalcoholic 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 disease [(1)]. Emerging evidence suggests that subjects with NAFLD have an increased risk of chronic kidney disease (CKD), as determined by a decline in the estimated glomerular filtration rate (eGFR) and/or microalbuminuria [(2,3)]. Routinely used measures of renal function, such as levels of blood urea nitrogen (BUN) and serum creatinine, increase significantly only after substantial kidney injury occurs and then with a time delay [(4)]. Therefore, novel biomarkers are needed for use in humans when early detection of kidney injury will influence therapy and potentially morbidity and mortality [(5)]. Preclinical and clinical studies showed that kidney injury molecule-1(KIM-1) is a potential marker of acute and chronic kidney injury [(6)]. It is not detectable in the normal kidney, but it is specifically upregulated in dedifferentiated proximal tubule cells after ischemic or nephrotoxic acute kidney injury (AKI) [(7)].

Aim of the Work

This study aimed to determine early renal functional alterations in overweight / obese children and adolescents with nonalcoholic fatty liver disease (NAFLD), as assessed by measuring urinary kidney injury molecule-1 level, and to evaluate its relation to the degree and various clinico-laboratory parameters of NAFLD.

2. Patients and Methods

This case control study was carried out upon 60 overweight o/ obese children and adolescents who were selected from those attending the outpatient clinics of the Pediatric Department of Tanta University Hospital. The work started in February 2018 up to February 2019.

Children were divided into two groups as: group I, 30 with nonalcoholic fatty liver (NAFLD) and group II, 30 without NAFLD. Diagnosis of NAFLD was based on the finding of hepatic steatosis detected by abdominal ultrasongraphy.

Inclusion criteria:

Children and adolescents with overweight or obesity. Their body mass index values will be in the 85th percentile or higher for age and sex.

Exclusion criteria:

1. Known disorders to cause fatty liver e.g. diabetes mellitus, glycogen storage disease and Wilson's disease.

2. Syndromic obesity.

3. Patients receiving long term use of drugs known to cause steatosis/ e.g. glucocorticoids.

4. Evidence of chronic liver diseases e.g. viral hepatitis and autoimmune hepatitis.

5. Known history, clinical, laboratory or imaging signs of renal disease**.**

Twenty healthy age-and-sex matched children with body mass index less than the 85th percentile for age and sex were chosen as controls. Eligibility.

2. Methods

Participants included in this study were subjected to the following:

A) Clinical Assessment:

1- Full history taking including history of drug intake and of any renal or liver disease.

2- Thorough complete physical examination including:

- Blood pressure measurement.
- Anthropometric measurements:
- Body weight and height.
- Body mass index (BMI): weight (kg)/ height (m2).
- Waist circumference (WC), hip circumference (HC) and waist to hip ratio (W/H ratio).

B) Laboratory Investigations:

1. Included total serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and prothrombin time (PT).

2. Lipid profile included total serum cholesterol level, triglycerides (TG), high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C).

3. Renal function tests including blood urea and serum creatinine.

4. Measurement of fasting plasma glucose level.

5. Measurement of fasting plasma insulin level. Using human insulin enzyme immunoassay (EIA) test kit according to manufacturer recommendations.

6. Assessment of insulin resistance.

7. Determination of microalbuminuria.

8. Measurement of urinary kidney injury molecule -1(KIM-1) levels [(8)]: Urine samples were collected aseptically directly into urine cups and stored. The kit used a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human Kidney injury molecule 1(Kim-1) in samples.

C) Abdominal ultrasonography:

The diagnosis of hepatic steatosis was made on the basis of characteristic sonographic features: increased echogenicity of the liver increased liver contrast compared to kidney, vascular blurring mainly of portal veins, and attenuation of echogenic level in deep seated area**.**

Statistical Analysis

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS V.20.

Results:

Subjects enrolled in this study were classified into two groups: group I, 30 obese overweight children with NAFLD and group II, 30 obese and overweight children without NAFLD compared with 20 healthy children.

Table (1) shows that

- No significant difference in mean values of age and sex percentage among the studied groups.

Table (1): Age and sex of the studied groups.

Variables		Group I (n=30)			Group II (n=30)			controls (n=20)		
Age (years)	Range	4.5	-	16	3.5	-	16.5	4.5	-	16
	Mean ±SD	9.733	±	2.769	9.717	±	3.334	9.125	±	2.955
	F			0.293						
	P-value			0.747						
Sex (%)	Male	13 (43.33%)			12 (40%)			9 (45%)		
	Female	17 (56.67%)			18 (60%)			11 (55.%)		
	F	0.136								
	P-value	0.934								

P-value: patients vs controls

F: Anova

Table (2): Anthropometric measures of the studied groups.

		Group I (n=30)			Group I (n=30)			Controls		
Height (cm)	**Range**	97	-	173	96.5	-	169	97	-	170
	Mean ±SD	140.200	±	18.292	139.450	±	18.040	135.525	±	18.300
	F			0.431						
	P-value			0.651						
Weight (kg)	**Range**	30	-	150	30	-	106	16	-	58
	Mean ±SD	68.293	±	31.322	62.840	±	22.634	31.875	±	10.076
	F			14.871						
	P-value			<0.001*						
	P1			0.660						
BMI (kg/m$^{2)}$	**Range**	24.25	-	54.4	25.4	-	42.4	13.2	-	20
	Mean ±SD	33.047	±	7.405	31.580	±	4.886	17.045	±	1.910
	F			57.772						
	P-value			<0.001*						
	P1			0.562						
Waist circumference (cm)	**Range**	68	-	140	55.5	-	118	24	-	75
	Mean ±SD	94.080	±	17.923	86.627	±	15.601	47.300	±	14.751
	F			53.761						
	P-value			<0.001*						
	P1			0.187						
Hip circumference (cm)	**Range**	75.5	-	162.5	65.2	-	129.6	32.8	-	137.7
	Mean ±SD	109.070	±	22.076	100.401	±	19.562	76.105	±	28.399
	F			12.743						
	P-value			<0.001*						
	P1			0.314						
Waist/Hip ratio	**Range**	0.8	-	0.95	0.8	-	0.95	0.4	-	0.76
	Mean ±SD	0.865	±	0.049	0.866	±	0.048	0.633	±	0.104
	F			91.449						
	P-value			<0.001*						
	P1			0.997						

* Significant. BMI: Body mass index. F: Anova. P- value: patients vs controls. P1: group (I) vs group (II)

- There were significant increase in the mean values of weight, BMI, waist circumference, hip circumference, W/H ratio in patients (group I, II) compared to controls.
- These values were no significant difference between subjects of group I and group II compared to controls regarding height values.
- No significant difference between group I and groupie regarding all these measurements.

Mean values of serum bilirubin, ALT, PT and serum albumin level showed no significant difference between group I, II and controls. Mean values of AST show significant increase in group (I, II) compared to controls but there is no significant difference between group (I) and (II). Mean values of ALP show significant increase in group (I, II) compared to controls and there is a significant increase in group (I) compared to group (II).

Mean values of total cholesterol, triglycrides and LDL levels was significantly higher in subjects of (group I, II) compared to controls. Mean values of HDL level was significantly lower in (group I, II) compared to controls. No significant difference between group I and group II regarding all these laboratory data.

Mean values of FBS show no significant difference between the studied groups. Mean values of fasting serum insulin and IR show a significant increase in subjects (group I, II) compared to controls and a significant increase in group (I) compared to group (II).

Mean values of blood urea and serum creatinine, show no significant difference in subjects (group I, II) compared to controls. Mean values of urine albumin was not significant between subjects (group I, II) compared to controls and also between group I and group II.

Urinary KIM-1 of the studied subjects:

Table (4) and figure (1) show that:

- Mean values of urinary KIM-1 was comparable between the studied groups.

- Mean values of urinary KIM-1 of group (I) was higher than group (II) but not statistically significant (p>0.005).

Table (3): Comparison of laboratory data of the studied group.

		Groups									ANOVA		TUKEY'S Test		
		Group I			Group II			Group III			F	P-value	I & II	I & III	II & III
ALT (U/L)	Range	10	-	96	6	-	95	6	-	55	2.121	0.127			
	Mean ±SD	31.067	±	22.220	25.233	±	17.828	20.300	±	11.499					
AST (U/L)	Range	11	-	58	8	-	48	8	-	35	6.531	0.002*	0.211	0.002*	0.098
	Mean ±SD	30.000	±	12.080	25.200	±	11.445	18.600	±	7.843					
ALK (U/L)	Range	80	-	250	66	-	186	45	-	150	30.632	<0.001*	0.021*	<0.001*	<0.001*
	Mean ±SD	153.133	±	35.237	131.200	±	32.053	83.450	±	20.857					
Prothrombine time S	Range	8	-	16	9	-	16	9	-	16	1.504	0.229			
	Mean ±SD	12.200	±	2.091	12.733	±	2.100	11.700	±	2.055					
HDL (mg/dl)	Range	33	-	89	30	-	97	41	-	95	11.397	<0.001*	0.820	<0.001*	<0.001*
	Mean ±SD	51.273	±	13.780	53.617	±	16.015	70.900	±	15.546					
LDL (mg/dl)	Range	65	-	158	36	-	150	45	-	99	7.734	0.001*	0.320	0.001*	0.028*
	Mean ±SD	103.567	±	22.320	95.273	±	25.390	78.550	±	15.415					
Cholesterol (mg/dl)	Range	108	-	230	95	-	238	77	-	186	9.613	<0.001*	0.557	<0.001*	0.004*
	Mean ±SD	170.067	±	33.412	160.833	±	37.359	127.450	±	31.640					
Triglyceride (mg/dl)	Range	59	-	290	50	-	235	75	-	163	0.041	0.960			
	Mean ±SD	125.000	±	46.741	121.907	±	47.037	122.950	±	23.437					
Fasting blood glucose (mg/dl)	Range	64	-	115	60	-	117	68	-	112	1.175	0.314			
	Mean ±SD	90.333	±	12.226	86.800	±	13.402	84.950	±	12.605					
Fasting serum insulin level (mclu/ml)	Range	4.1	-	24.1	3.19	-	28.1	3.2	-	14	21.214	<0.001*	0.948	<0.001*	<0.001*
	Mean ±SD	15.041	±	4.971	14.662	±	5.326	6.930	±	3.016					
Insulin resistance	Range	3.2	-	5.7	2.43	-	6.44	0.57	-	3.04	115.465	<0.001*	0.727	<0.001*	<0.001*
	Mean ±SD	4.487	±	0.689	4.339	±	0.809	1.468	±	0.753					
Urea (mg/dl)	Range	8	-	40	10	-	35	9	-	18	7.248	0.001*	0.935	0.002*	0.005*
	Mean ±SD	22.267	±	9.262	21.567	±	8.369	14.300	±	2.736					
Creatinine (mg/dl)	Range	0.1	-	0.9	0.1	-	0.88	0.11	-	0.8	0.614	0.544			
	Mean ±SD	0.415	±	0.231	0.397	±	0.218	0.347	±	0.185					
Albumin in urine (mg)	Range	30	-	150	44	-	220	40	-	240	2.463	0.092			
	Mean ±SD	99.300	±	30.739	115.767	±	40.326	124.550	±	54.735					

Table (4): Comparison between the studied groups in urinary KIM-1.

KIM-1 (ng/ml)	Groups									ANOVA	
	Group I			Group II			Group III			F	P-value
Range	0.24	-	2.9	0.56	-	2.9	0.6	-	2.4	0.493	0.613
Mean ±SD	1.442	±	0.719	1.288	±	0.744	1.285	±	0.465		

Ultrasonographic Grading Of Hepatic Steatosis:
Table (5) and show that:

Degree of fatty infiltration of group (I) (n=30) was found as follows:

Grade I steatosis was found in 16 (53.33%) children.

Grade II steatosis was found in 9 (30%) children.

Grade III steatosis was found in 5 (16.67%) children.

Table (6) shows that:

- Urinary KIM-1 is correlated significantly to the following variables: waist / hip ratio, serum alkaline phosphatase, serum triglycrides and insulin resistance.

Table (5): Ultrasonographic grading of hepatic steatosis of group (1) (n = 30):

Grade of steatosis	N	%
I	16	53.33
II	9	30.00
III	5	16.67
Total	30	100.00

Correlations between urinary KIM-1 and demographic, anthropometric and laboratory data:

Table (6): Correlations between urinary KIM-1 and demographic, anthropometric and laboratory data:

Correlations		
	KIM-1 (ng/ml)	
	R	**P-value**
Age (years)	0.374	0.036
Weight (kg)	0.385	0.005
Height (cm)	0.426	0.006
BMI	0.264	0.047
Systolic BP	0.276	0.077
Diastolic BP	0.250	0.056
Waist circumference (cm)	0.217	0.096
Hip circumference (cm)	0.176	0.179
Waist/ Hip ratio	0.332	0.010*
ALT (U/L)	0.081	0.540
AST (U/L)	0.098	0.455
ALP (U/L)	0.321	0.013*
Prothrombine time S	-0.006	0.964
HDL (mg/dl)	-0.264	0.041
LDL (mg/dl)	0.151	0.248
Cholesterol (mg/dl)	-0.049	0.711
Triglyceride (mg/dl)	0.331	0.010*
Fasting blood glucose (mg/dl)	0.270	0.057
Fasting serum insulin level (µU/ml)	0.185	0.156
Insulin resistance	0.266	0.040*
Urea (mg/dl)	0.025	0.847
Creatinine (mg/dl)	0.201	0.123
Albumin in urine (mg)	0.038	0.0771

4. Discussion

In this study diagnosis of overweight and obesity was based on using body mass index (BMI) which is accepted as a standard measure of overweight and obesity for children two years of age and older [10].

No significant difference in BMI values was found between overweight / obese children with NAFLD and those without steatosis. This agrees with the study of **Uslusoy et al** [11] who detected that there was no relation between steatosis and BMI in obese patients. Also, **Boza et al** [12]found that no significant association between BMI and hepatic histological changes in NAFLD patients. Also no significant correlation between BMI values and degree of hepatic steatosis in obese NAFLD patients was observed in our study.

Measurement of waist circumference, hip circumference and W/H ratio were not significantly different between those having NAFLD and those without. However, this ratio was significantly correlated with the degree of steatosis. Waist circumference is considered a surrogate measure of viscral fat and may predict the development of NAFLD in children [13]. Our finding is in agreement with that found by previous works [14-15-16]**. Zhang et al** [14] evaluated 332 obese children with and without NAFLD, and found that the W/H ratio presented an optimal cutoff point for the prediction of NAFLD of 0.62. **Lee Yung et al** [15] identified W/H ratio as a sensitive indicator for risk of NAFLD Also, **Singh et al** [16] signified that W/H ratio is an independent predictor of liver damage in patients with NAFLD.

In the present study liver function tests revealed higher serum transeaminases (ALT-AST) and alkaline phosphatase (Alp) levels in group I and II obese /overweight subjects compared to controls. Serum levels of transaminases are comparable in obese/overweight subjects with and without NAFLD. However, serum ALp was significantly higher in NAFLD patients than obese/overweight without NAFLD.

Similar findings were reported in other studies [17-18]. **López et al** [17] found elevation of serum (ALT), (AST) and (ALp) levels in their study of patients with fatty liver. **Nirmal et al** [18] found ALT elevation in NAFLD patients compared to controls. We found that

serum alkaline phosphatase was significantly correlated with grades of hepatic steatosis. This conicides with the study done by **López et al** [17]. However, serum transaminases (ALT, AST) were not significantly correlated with the degree of NAFLD and this agrees with the study conducted by **Franzese et al** [19].

Lipid profile, in the present work, showed abnormal values in obese/overweight children compared to controls with no significant difference between subjects with NAFLD (group I) and without NAFLD (group II). Serum triglycrides and LDL level correlated significantly with the degree of hepatic steatosis. Variable results were obtained by other studies Kirovski **et al** [20] found no significant increase in cholesterol, triglycrides, HDL and LDL concentrations between subjects with and without NAFLD.

Rousch et al, Martinez et al and **Cabrerizo et al** [21-22-23] found hypertriglyceridemia in NAFLD obese children. The current study showed elevated serum fasting insulin and insulin resistance (IR) as assessed by HOMA-IR in obese/overweight children compared to controls. Higher values were detected in NAFLD patients than obese subjects without NAFLD. Moreover, fasting serum insulin and IR correlated significantly with the degree of steatosis. These findings conicide with that shown by **Burgert et al** [24] **Cordeiro et al** [25] and **Gabriela. V.C** [26].

Measurement of urinary albumin, in our work, showed comparable levels in the study subjects and controls. Also, no significant correlation was detected between urinary albumin levels and degree of hepatic steatosis. In consistence to our findings **Lin et al** [27] found low grade albuminuria in middle age Chinese patients with NAFLD. **Yilmaz et al** found that [28]NAFLD patients with microalbuminuria had a remarkably higher fibrosis score than those without. This supports our finding and indicating no significant association between severity of hepatic lesion induced by fatty infiltration and degree of albuminuria.

In contrast, some studies showed significant albuminuria in NAFLD patients [29-30]. **Hwang et al** [29] revealed a strong relationship between microalbuminuria in NAFLD prediabetic patients. **Sun et al** [30] showed that hepatic steatosis is associated with increased urinary albumin excretion and prevalence of CKD in Asian population. A meta analysis study by **Wijarnpreech** [31] showed a significantly increased risk of albuminuria among patients with NAFLD independent of baseline confounding factors.

In the current study, assessment of kidney injury molecule -1 (KIM-1) in urine of the studied subjects with normal blood urea and creatinine levels, demonstrated no significant difference in its level between both groups obese /overweight children and controls. There was an apparent increase in urinary KIM-1 level in NAFLD patients compared to those of obese subjects without NAFLD, yet this increase of this molecule is not statistically significant ($p>0.05$).

Applying the urinary KIM-1 levels to the degree of hepatic steatosis clearly showed a significant rise in the level of this molecule with increasing the grades of ultrasonographic echogenicity of the studied NAFLD patients. **Zulu** et al [32] compared the levels of urine KIM-1 in 80 Zambian individuals with and without kidney disease. They found no significant difference in KIM-1 level between the kidney diseased group and controls. In a met-analysis based on ten studies, Zhou **et al** [33] reported that a borderline significance of uKIM-1 in predicting CKD stage 3 in the community-based population was observed.

Other studies showed a significant rise of uKIM-1 in kidney diseases. **Lobato et al** [34] showed that urinary KIM-1 could reflect early kidney damage and thus provides a window for early clinical intervention. The study was conducted on 250 adult patients representing the five stages of CKD. KIM-1 was associated with loss of kidney function and progression to more advanced stages of CKD. Thus, as the rated tertile increased, there was an increased incidence of renal function loss, which was statistically significant for KIM-1. Unlike our study, their participants were elder with larger in number and renal affection was of different severities.

De Silva et al [35] demonstrated that urinary KIM-1 is capable of detecting early renal damage in the absence of albuminuria. They also reported significantly higher KIM-1 levels in apparently healthy farmers in chronic kidney disease endemic area (in Sri Lanka) in comparison to controls. These observations may indicate possible early renal damage in absence of persistent albuminuria and potential capabilities of urinary KIM-1 in early detection of renal injury. In agreement to our work, where uKIM-1 did not correlate with proteinuria, **Zhang et al** [36] found in their researches that KIM-1 expression correlated positively with interstitial damage, but did not correlate with proteinurea. Finally, the present work showed, in the studied NAFLD children with normal baseline kidney function tests, that there was no significant change in urinary KIM-1 level in NAFLD compared to obese /overweight non NAFLD subjects. However, a remarkable increase of this biomarker was evident in the advanced grades of hepatic steatosis (grade III).

Correlation analysis revealed significant association between uKIM-1 and waist/hip ratio, serum alkaline phosphatase, triglycrides and insulin resistance values. These multiple covariates that are associated with uKIM-1, as an index of renal injury,

are considered risk factors contributing to the damage of kidney function in the studied children and adolescents with fatty liver. This finding is supported by the researches done by **Lie et al** [37] and **Jin et al** [38]. Advanced hepatic pathological processes in NAFLD (in grade III steatosis in our study) and the coexisting consequences (abnormal lipid profile and insulin resistance) appeared to be linked to the enhancement of renal function impairment as shown in the current work with the strong correlations between these risk factors and excretion of KIM-1 in urine of NAFLD children and adolescents.

Conclusion

The current study showed that:

- Urinary KIM-1 is not significantly different between NAFLD and non NAFLD subjects.
- Urinary KIM-1 correlated significantly to the degree of hepatic steatosis.
- Urinary albumin level was not significantly different between NAFLD and non NAFLD obese children.
- Grades of hepatic steatosis I (16, 53%), II (9,30) and III (5, 17%).
- Urinary KIM-1 was significantly correlated with waist/hip ratio, serum alkaline phosphatase, triglycrides, and insulin resistance values.
- There was no significant correlation between uKIM-1and albumin in urine.

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