Evaluation of serum leptin and adiponectin and their associations with obesity-related renal injury among Egyptian adolescents

Azza A El-Shaheed[a], Reham F. Fahmy[a], Nermine N. Mahfouz[a], Salwa R El-Zayat[b], Hiba Sibaii[b], Rehab S.I. Moustafa[a]

[a]Department of Child Health, [b]Medical Physiology, Medical Research and Clinical Studies Institute, National Research Centre, Giza, Egypt

Correspondence to Reham F. Fahmy, PhD, Child health, Child Health Department, Medical Research and Clinical studies Institute, National Research Centre, 33 El Bohouth Street, Dokki, POB 12311, Giza, Egypt.
Tel: 01001236323;
e-mail: Reham_dodo2@yahoo.com

Received: 6 July 2023
Revised: 31 July 2023
Accepted: 9 August 2023
Published: 26 December 2023

Journal of The Arab Society for Medical Research 2023, 18:134–141

Background/aim
Childhood obesity has come to be a worldwide epidemic. Current epidemiological data advocate that obesity is linked with an increased threat of renal injury in children. Early markers will be beneficial in the prevention of renal injury.
The present study aimed to assess serum levels of leptin and adiponectin and their associations with comorbidities of obesity to examine their potential effects on obesity-related renal injury among Egyptian overweight/obese adolescents. In addition, the study aimed an analysis of the kidney injury molecule-1(KIM-1) to identify the early renal effect of obesity.
Subjects and methods
A case–control study was conducted on 45 Egyptian overweight/obese adolescents aged 10–18 years of both sexes and 44 age- and Sex-matched healthy individuals. Serum fasting glucose and insulin were analyzed, and a homeostasis model assessment of insulin resistance was calculated. Serum leptin, adiponectin, and KIM-1 were measured using ELISA techniques.
Results
The overweight/obese group had significantly higher KIM-1 and leptin levels, and lower adiponectin levels in comparison to the control group ($P=<0.05$). Serum adiponectin levels had significant negative correlations, with both systolic ($r=-0.480$, $P=0.013$) and diastolic ($r=-0.491$, $P=0.011$) blood pressure, while serum leptin levels did not correlate with BMI, systolic blood pressure, diastolic blood pressure, HOMA- IR, eGFR, or KIM-1 in the study group ($P>0.05$).
Conclusion
Leptin and adiponectin are the main pathogenic factors for renal injury in obese adolescents.

Keywords:
adolescents, leptin, kidney injury molecule-1 (KIM-1), obesity, renal injury

J Arab Soc Med Res 18:134–141

1687-4293

Introduction

Childhood obesity is rapidly growing as a global epidemic, and the ailment of being overweight/obese remains and carries on to adolescence [1]. A sedentary lifestyle [2] and undesirable dietary behaviors [3] are the key predisposing factors of obesity among adolescents.

The rise in the frequency of chronic kidney disease (CKD) has been associated with a significant increase in obesity, which is an effective risk factor for the occurrence of kidney injury. Obesity increases the threat of developing chief risk factors for CKD, such as hypertension and diabetes, and it has a direct effect on the occurrence of CKD and end-stage renal disease (ESRD) by itself [4]. It is supposed that a certain degree of renal impairment related to obesity starts early in childhood, long before the emergence of diabetes, hypertension, and other related comorbidities recognized to confer to renal disease [5].

Though the molecular mechanisms that correlate obesity and CKD are not well defined, the contribution of adipose tissue (AT) is becoming progressively significant in obesity-related kidney damage [6]. Adipose tissue has come out as an exceedingly active endocrine organ, depending on its capability to produce an excess of biologically active adipokines, for instance, adiponectin, leptin, interleukin-6 (IL-6), or tumor necrosis factor alpha (TNF-α) that are incorporated in a wide range of physiological processes [7]. In the setting of obesity,

lipotoxcity and the change in the secretion profile of AT provoke inflammation, oxidative stress, and fibrosis in the kidney, which eventually result in impairment of renal function [6]. The existence and severity of CKD are commonly centered on the glomerulus and given that proximal tubules comprise 90% of the cortical mass of the kidney, tubule intersitial lesions are largely more sensible than glomerular lesions in anticipating the progression of renal disease [8]. Kidney injury molecule-1 (KIM-1) is a membrane protein that is not noticeable in the serum/urine of healthy individuals. However, KIM-1 is broadly expressed in cells of the proximal tubule after ischemia, and toxic circumstances and has been stated to be a proper marker in the diagnosis of acute kidney injury (AKI) [9]. Moreover, current studies also advocated urinary KIM-1 as a biomarker for the evaluation of nephropathy in several chronic kidney diseases [10].

Obesity-associated renal disease is asymptomatic, insidious, and difficult to diagnose. The known biomarkers of the kidney, involving blood urea nitrogen, serum level of creatinine (sCr), and urine albumin/protein ratio do not alter rapidly through the exhibition of acute conditions and become changed later through the course of the disease [11].

Consequently, apprehension of the deleterious effects on the adipo- renal axis is important to cease the development and progress of chronic kidney disease; furthermore, suitable biomarkers are required for early diagnosis of obesity-associated renal damage [11].

The present study aimed to assess serum levels of leptin and adiponectin and their associations with comorbidities of obesity to examine their potential effects on obesity-related renal injury among Egyptian overweight/obese adolescents. The study also assessed the role of the kidney injury molecule-1(KIM-1) in defining the early renal effect of obesity.

Subjects and methods

Subjects

A case–control study was carried out on 89 Egyptian adolescents aged 10–18 years of both sexes. The cutoff BMI was calculated according to the World Health Organization (WHO) growth charts.

Inclusion criteria

Adolescents of both sexes aged from 10 to 18 years old with normal renal function.

Exclusion criteria

Adolescents who have a genetic syndrome or other endocrine disorder known to cause obesity (e:g. Prader-Willi syndrome, hypothyroidism, Cushing's disease). Overweight/obese adolescents were recruited from the Nutrition- Immunotherapy Clinic at the Medical Research Centre of Excellence, and the control group was recruited from the pediatric outpatient clinic.

Study design

The study participants were divided into two groups as follows:

Group A (the study group): Included 45 overweight/obese adolescents with BMI more than or equal to 85th centile.

Group B (the control group): Involved 44 healthy normotensive age- and Sex-matched adolescents who had a BMI below the 85th centile.

Ethical approval

The present study was carried out in accordance with the Code of Ethics of the World Medical Association, consistent with the principles stated in the Declaration of Helsinki. The study was approved by the 'Ethics Committee of National Research Centre, Cairo, Egypt' under approval number 16/130. An informed written consent was attained from the legal guardian of every participant before participation in the study.

Methods

The study participants were subjected to the following

History and physical examination

History taking with emphasis on age, sex, parent education, the inquiry about associated morbidities such as diabetes mellitus, hypertension, and family history of obesity, diabetes mellitus, and hypertension.

Physical examination with special emphasis on weight, height, waist, hip circumference measurements, and blood pressure measurement.

Anthropometric measures

Body weight was measured with light clothes and barefoot on Seca Scale Balance to the nearest 0.1 Kg. Height was measured to the nearest 0.5 cm on a Holtain portable anthropometer. Calculation of BMI was done using the equation [weight (Kg)/height (m^2)]. Data were plotted on WHO curves using the software AnthroCale v1.66 Home [12]. Waist circumference was measured at the midpoint between the iliac crest and the rib cage on the midaxillary line using a flexible and inelastic tape. Hip circumference was measured around the largest part of the hips (the widest part of the buttocks). Blood

pressure was measured after a 5-min rest in the semi-sitting position with an appropriately sized cuff using a Riester sphygmomanometer made in Germany. Data were plotted through the software AnthroCale v1.66 Home, and the participants were diagnosed to have hypertension consistent with the guidelines of the American Academy of Pediatrics, (AAP), 2017 [13].

Biochemical investigations

Blood was drawn in the morning after overnight fasting (at least 8 h). Blood samples were centrifuged at 350×g for 3 min, and then serum was isolated. Blood glucose, insulin, creatinine, and uric acid were measured immediately and the other parts of the serum were stored at −20° until the other laboratory analysis.

Serum uric acid and creatinine were assessed by the colorimetric method using kits of Biodiagnostic Co (Egypt). Schwartz formula was used to calculate the estimated glomerular filtration rate (eGFR) [14]. Insulin resistance was estimated from fasting plasma measurements using the homeostasis model assessment of insulin resistance (HOMA- IR) using the formula: [fasting insulin (μU/ml)× fasting glucose (mg/dl)/405] according to Mathews *et al.* [15]. The criteria of insulin resistance were HOMA- IR > 4.0 for adolescents [16].

Serum leptin, adiponectin, and KIM-1 were assessed using commercially available enzyme-linked immunosorbent assay (ELISA) kits, where leptin and adiponectin were measured using kits of NOVA Co, (Beijing, China), while KIM-1 was measured using kits of Aviscera Bioscience Co (Santa Clara, CA, USA).

Statistical analysis

Data entry and analysis were executed by the Statistical Package for the Social Sciences (SPSS) software, version 16. Data were shown as mean and standard deviation (SD). Independent sample t-test was used for comparison between groups for parametric data. Pearson's correlation [Correlation Coefficient (r)] was used for the assessment of correlations. *P* value <0.05 was considered statistically significant.

Results

The study group included six overweight and 39 obese adolescents. The two groups were well matched as regards age and Sex (*P*=0.446 and *P*=0.267, respectively). Hip circumference, waist circumference, and waist/hip ratio were significantly higher in the overweight/obese group in comparison to the control group (*P*=0.001). Systolic and diastolic blood pressure centiles were significantly higher in the study group in comparison to the control group (*P*=0.005, *P*=0.019, respectively). Four of the study group have missed blood pressure readings and 13 of them were diagnosed to have stage 1 hypertension according to AAP, 2017 Criteria. The control group was normotensive. The demographic and clinical data of the study participants are shown in Table 1.

Serum creatinine and uric acid values of both groups were all within normal limits, but the mean serum level of creatinine was significantly higher in the study group in comparison to the control group. All participants had normal glomerular filtration rates consistent with the Schwartz formula. Fasting blood glucose levels for all participants were <126 mg/dL. In the study group, 38 participants had HOMA-IR values and 8 of them had insulin resistance (21.1%) (HOMA-IR mean ±SD=2.72±2.57). HOMA-IR in the study group was higher than in the control group but was on the border of statistical significance (*P*=0.05) as shown in Table 2.

Table 1 Demographic and clinical data of the study participants

	Group A (overweight/obese)	Group B (nonobese)	*P values*
Sex (male/female)	13/32	17/27	0.267
Age (years)	13.05±2.61	12.62±2.60	0.446
Weight (Kg)	73.41±18.26	37.39 ±10.68	0.001*
Weight centile	96.26±4.80	27.43±25.05	0.001*
Height (cm)	154.16±10.65	146.05±13.04	0.002*
Height centile	51.50±28.89	32.60±28.74	0.003*
BMI	30.55±5.61	17.22 ±2.71	0.001*
BMI centile	98.30±2.68	34.40±28.16	0.001*
Waist circumference (cm)	89.17±12.66	60.68±8.18	0.001*
Hip circumference (cm)	103.56±13.91	75.62±11.30	0.001*
Waist/hip ratio	0.86±0.06	0.81±0.06	0.001*
Systolic blood pressure centile	52.95±32.60	31.66±22.64	0.005*
Diastolic blood pressure centile	65.93±28.52	54.32±21.49	**0.019***

*Significant difference at *P*<0.05 using Student's t-test.

Mean serum levels of leptin were significantly higher, while mean serum levels of adiponectin were significantly lower in the study group in comparison to the control group ($P<0.05$). Moreover, the study group had significantly higher mean serum levels of KIM-1 in comparison to the control group ($P=0.001$). The biochemical data of the study participants are shown in Table 2.

No significant difference could be detected between overweight/obese adolescents who were hypertensive and those who were normotensive as regards KIM-1 and leptin ($P=0.759$, $P=0.408$, respectively) as shown in Table 3.

Serum leptin levels did not correlate with BMI, systolic blood pressure, diastolic blood pressure, HOMA- IR, eGFR, or KIM-1 in the study group ($r=0.203$, $P=0.258$, $r=0.122$, $P=0.513$, $r=-0.063$, $P=0.734$, $r=-0.025$, $P=0.902$, $r=-0.128$, $P=0.493$, $r=0.181$, $P=0.331$, respectively) as shown in Table 4.

Serum adiponectin levels had significant negative correlations with both systolic and diastolic blood pressure ($r=-0.480$, $P=0.013$, $r=-0.491$ $P=0.011$, respectively), while, no significant correlations could be detected between it and either BMI, eGFR, or HOMA-IR in the study group ($r=-0.139$, $P=0.482$, $r=-0.107$, $P=0.634$, $r=0.065$, $P=0.768$, respectively) as shown in Table 5.

Discussion

Childhood obesity has become a significant health issue globally. Recent epidemiological data propose that obesity is correlated to the raised threat of childhood renal injury. A high BMI is one of the threat factors for new-onset CKD [17]. Furthermore, obesity may impact progress to renal failure in patients affected by early stages of renal disease [18].

The study showed that waist and hip circumferences were significantly higher in the study group compared with the control group. Waist circumference (WC) was displayed as a proper measure of overweight and its comorbidities [19]. In addition, WC was defined to be a proper measure of visceral adipose tissue and abdominal obesity that are more closely associated with cardiovascular risk than overweight as evaluated by BMI per se [20]. The study also showed that the overweight/obese group had significantly higher systolic and diastolic blood pressure centiles in comparison to the control group. This is in agreement with other studies such as the Özlem *et al.* [11], Azza [21] and Goknar *et al.* [22] studies, which stated that obese children and adolescents had significantly higher systolic and diastolic blood pressures.

Hypertension is considered one of the utmost common comorbid conditions linked with obesity which is a main risk factor for CKD. Epidemiological studies

Table 2 Biochemical data of the study participants

	Group A (overweight/obese)	Group B (nonobese)	*P values*
Creatinine (mg/dl)	0.94±0.23	0.79±0.21	0.007*
Uric acid (mg/dl)	5.27±1.31	4.89±1.10	0.159
Fasting blood glucose (mg/dl)	92.27±8.78	90.40±9.64	0.347
KIM-1(ng/ml)	4.49±1.30	2.42±1.39	0.001*
Leptin (pg/ml)	282.74±143.49	96.35±26.24	0.003*
Adiponectin (ng/ml)	0.51±0.23	1.47±0.74	0.001*
HOMA-IR	2.72±2.57	1.19±1.16	0.050*

*Significant difference at $P<0.05$, using Student's t-test.

Table 3 Comparison between overweight/obese adolescents who were hypertensive and those who were normotensive as regards KIM-1 and leptin

	Hypertensive overweight/obese (Number=13)	Normotensive overweight/obese (Number=28)	*P values**
Leptin (pg/ml)	181.82± 91.00	217.95±211.70	0.408
KIM-1 (ng/ml)	4.60±1.13	4.45±1.46	0.759

*Insignificant difference at $P>0.05$, using Student's t-test.

Table 4 Correlations between leptin and other variables in overweight/obese group

	Variables	Correlation coefficient (r)	*P values*
Leptin	Body mass index	0.203	0.258
	Systolic blood pressure	0.122	0.513
	Diastolic blood pressure	–0.063	0.734
	HOMA-IR	–0.025	0.902
	eGFR	–0.128	0.493

Table 5 Correlations between adiponectin and other variables in the overweight/obese group

	Variables	Correlation coefficient (r))	*P values*
Adiponectin	Body mass index	–0.139	0.482
	Systolic blood pressure	–0.480	0.013*
	Diastolic blood pressure	–0.491	0.011*
	HOMA-IR	0.065	0.768
	eGFR	–0.107	0.634

*Significant difference at $P<0.05$ using Pearson's correlation.

designate that 65–75% of primary (essential) hypertension is due to overweight or obesity [23]. Obesity-related hypertension is a multifactorial complex disease that involves the activation of the renin–angiotensin–aldosterone system (RAAS), changed vascular function, and increased sympathetic nervous system (SNS) [24]. Insulin resistance per se, or accompanied by hyperleptinemia, stimulates the SNS, which results in vasoconstriction and decreased blood flow of the kidney, resulting in stimulation of RAAS and sodium and water retention [25]. Furthermore, new reports display that additional mechanisms might be implicated in the pathogenesis of hypertension in obese children, for example, proinflammatory cytokines and oxidative stress pathway. These signaling pathways probably participate in the augmented stiffness of arteries and dysfunction of the endothelium [26]. Increased alertness is required for early diagnosis of obesity-associated hypertension in adolescents to decrease the threat of associated comorbidities, for instance, CKD.

The present study showed that many overweight/obese groups had insulin resistance. This is in agreement with other studies. Özlem and colleagues [11] and Marko and colleagues [27] stated that obese adolescents had a statistically significant higher frequency of insulin resistance. Studies have revealed that obesity frequently goes together with insulin resistance, particularly visceral obesity. It has been proposed that hyperinsulinemia and insulin resistance could prompt hypertrophy of the glomeruli, directly or indirectly, through activation of the insulin-like growth factor-1 receptor [28]. Insulin resistance is also related to microalbuminuria, thus, several authors have proposed that insulin resistance could be a link between obesity and CKD [28,29].

The study showed that the mean serum level of KIM-1 in overweight/obese adolescents was significantly higher than in the control group. This is in agreement with other studies. Goknar *et al.* [22] and Polidori *et al.* [30] stated that obese children had higher levels of KIM-1 in urine in comparison to the control group. Since its discovery, KIM-1 has risen as a sensible biomarker of tubular injury. Upregulation of KIM-1 is a known result of injury of proximal tubules in the nephron [31]. Furthermore, it has been also shown that the study of the expression of KIM-1 could be beneficial in the demonstration of injury of glomeruli [32].

The suggested mechanisms of raised KIM-1 expression level in acute tubular injury are with injury, the polarity of the tubular cell is absent, so KIM-1 might be directly released into the interstitium. In additionally, augmented transepithelial permeability after injury of tubules results in a back leak of tubular contents into the circulation [33]. Expression of KIM-1 has also been revealed in samples of urine and biopsies of kidney of patients with CKD from a number of causes and it is an appropriate marker for chronic kidney damage that antecedes the worsening of kidney function [34].

The stimulus for the expression of KIM-1 and its presence in the urine in CKD are probably associated with local hypoxia and nephrotoxic outcomes of mediators of kidney injury [35]. The significance of KIM-1 comes from its capability to specifically confine the specific site of kidney injuryThe raised levels of KIM-1 may antecede histological changes in patients with acute kidney injury [36] and the presence of KIM-1 in urine has been displayed as a proper interpreter of renal injury before the appearance of obvious alterations in eGFR [37], in addition to its capability to expect the long-term prognosis of chronic kidney disease [38]. So, KIM-1 displays a promise to be a blood biomarker that especially reveals acute and chronic kidney injury.

Although hypertension is a risk factor for renal injury, we found that the mean serum level of KIM-1 was not significantly increased in the hypertensive overweight/obese group compared with nonhypertensive ones. Similarly, Goknar and colleagues [22] stated that hypertensive obese participants did not have significantly higher KIM-1 in urine in comparison to obese subjects with normal blood pressure.

The mean serum levels of leptin was found to be significantly higher in the overweight/obese group in comparison to the control group. Similarly, Edward and colleagues [39] found that leptin levels were significantly increased in obese children. Leptin is principally released by adipose tissue proportionally to the volume of stores of body fat. Circulating levels of leptin relate thoroughly with the total volume of body fat being, consequently, raised in obese individuals [40].

Obesity and associated chronic unresolved inflammation result in lipotoxicity, dysfunction of adipose tissue, and dysregulation of the secretion profile of the adipose tissue, which might impact renal function during obesity [6].

Owing to the effective several impacts of leptin, hyperleptinemia can be implicated in the pathogenesis of obesity and its associated disorders. It was proposed that leptin could have a contribution to the pathogenesis of obesity-associated glomerulopathy in obese patients [41]. Leptin can regulate diverse signaling pathways in the kidney, as mesangial and glomerular endothelial cells prompt profuse receptors of leptin. Leptin produces an augmented expression of profibrotic genes, for instance, transforming growth factor-beta (TGF-ß1), and proinflammatory cytokines. TGF-ß1 is an effective motivator of the proliferation of mesangial cells in the kidney. A rise in these molecules might result in the accumulation of the extracellular matrix, thickening of the basement membrane of glomeruli, and glomerular mesangial hypertrophy, causing sclerosis of glomeruli and proteinuria [42]. Moreover, leptin can also be indirectly implicated in the injury of the kidney through the involvement of hyperleptinemia in obesity-related hypertension through the overactivation of the sympathetic nervous system [43]. The present study showed that there was no significant difference between the hypertensive overweight/obese group and nonhypertensive ones as regards the mean serum level of leptin. Also, there were no significant correlations between serum leptin levels and systolic and diastolic blood pressure. Similarly, Hossein and colleagues [44] stated that systolic and diastolic blood pressures had no association with serum levels of leptin among obese children. There is a scarcity of studies that examined the assumed association between serum levels of leptin and blood pressure among obese adolescents and their results have not been compatible [45].

Serum leptin levels did not significantly correlate with BMI, HOMA-IR, or eGFR in the study group. Similarly, Edward and colleagues [39] stated that leptin was not correlated with GFR decline, which is in diversity with previous reports. For instance, Daschner and colleagues [46] stated that GFR was an independent weak predictor of serum leptin in a cohort of 134 children who have renal disease. The divergence between the results might be accredited to the fact that our obese adolescents had normal eGFR and that the relevant influence of renal function on increased levels of leptin is more prominent with progressive CKD and not in patients with mild-to-moderate CKD [39].

Widecka and colleagues [47] stated no association between leptin and insulin resistance index. The literature reports on this issue are indecisive.

The study showed that the mean serum levels of adiponectin was significantly lower in the study group compared with the control group. This was in agreement with other studies. Asayama and colleagues [48] and Christine Frithioff and colleagues [49] found that overweight and obese children showed lower adiponectin levels compared with the control. Adiponectin is a 30-KDa plasma protein that is mostly produced through the adipose tissue. Levels of adiponectin are negatively related to body fat proportion, and levels of adiponectin are reduced significantly in obesity [50]. There is no clear understanding of why adiponectin is decreased in those with increased fat mass in spite that it is produced by the adipose tissue. It is possibly through the inhibition of gene transcription of adiponectin [51]. Adiponectin was proposed to have a contribution in the pathogenesis of obesity-related glomerulopathy through receptors on podocytes having a role in podocyte morphology and/or function [18]. In mice lacking the expression of adiponectin, there was a noticed effacement of podocyte foot processes. In addition, hypoadiponectinemia results in tubular inflammation by reducing the activation of tubular AMP-activated protein kinase (AMPK), causing an accumulation of monocyte chemotactic protein (MCP)-1 that is included in the onset of inflammation in the kidney [52]. The study showed that adiponectin had significant negative correlations with both systolic and diastolic blood pressure. Similarly, Varda and colleagues [53] found a significant negative correlation between adiponectin and systolic blood pressure in obese children and adolescents with hypertension. Some clinical studies have demonstrated a correlation between concentration of plasma adiponectin and hypertension as hypoadiponectinemia is a risk factor for arterial hypertension. An inverse relationship was detected between mean diastolic pressure and concentration of adiponectin [54].

No significant correlations could be detected between adiponectin and BMI, eGFR, or HOMA-IR in the overweight/obese group of our study. Varda and colleagues [53] found that adiponectin had a significant negative correlation with BMI in obese children and adolescents. Human omental adipocytes produced adiponectin that was inversely correlated with BMI [55]. Serum adiponectin was inversely associated with eGFR [56]. Hypoadiponectinemia in the state of obesity enhances the production of ROS, causing oxidative stress in the podocytes that is probable to change the GFR [50]. It is postulated that adiponectin functions as an insulin-sensitizing

adipokine. Hypoadiponectinemia as a result of a high-fat diet has been intensely related to insulin resistance and metabolic syndrome [57]. Hotta and colleagues [58] reported coincident decreases in insulin action and levels of plasma adiponectin with the progression of obesity in rhesus monkeys. Though studies propose that adiponectin has an important role in regulating insulin sensitivity, the relation between them remains uncertain.

The absence of significant correlations in our study could be accredited both to the small-sized sample in our study and to the low rate of metabolic and hypertensive complications associated with obesity. Generally, there seemed to be an emergent relation between the dysregulation of adipokines in obesity and the development of renal injury.

Conclusion

The study showed that the overweight/obese group had significantly higher mean serum levels of KIM-1 and leptin, and significantly lower mean serum levels of adiponectin in comparison to the normal weight adolescent group. This study advocated that obese participants revealed a definite degree of renal damage before loss of kidney function as determined by changes in the secretion of adipokines, so leptin and adiponectin might be significant pathogenic factors for kidney injury in obese patients. KIM-1 might be used as a screening marker to reveal early damage of kidneys in obese adolescents to preclude the progress to irreversible renal inefficiency.

Acknowledgments

This research paper was a derivative from a cross-sectional research project entitled 'Early renal injury markers in obese adolescents,' under number 11010142 and funded by the National Research Centre (NRC) Egypt, in the 11th Research Plan of the NRC from 2016 to 2019.

Author's contributions: Azza Abd El-Shaheed was responsible for the conception, design, project administration, and supervision in addition to the manuscript revision. Reham F. Fahmy contributed to anthropometric assessments, clinical history taking, data entry, and writing the manuscript in addition to the submission of the manuscript to the journal. Nermine N. Mahfouz contributed to conception, design, project administration, anthropometric assessments, clinical history taking, and data entry. Salwa Refat El-Zayat was responsible for laboratory investigations and interpretations. Hiba Sibaii was responsible for laboratory investigations and interpretations. Rehab S.I.Moustafa contributed to anthropometric assessments, clinical history taking, and data entry. All authors read and approved the final manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Ding W, Cheung WW, Mak RH. Impact of obesity on kidney function and blood pressure in children. World J Nephrol 2015; 4:223–229.

2 Donnelly TT, Fung TS, Al-Thani A-AbM. Fostering active living and healthy eating through understanding physical activity and dietary behaviours of Arabic-speaking adults: a cross-sectional study from the Middle East. BMJ 2018; 8:e019980.

3 El-Shaheed AA, Mahfouz NN, Moustafa RSI, Elabd MA. Alarming eating behaviours among adolescents in Egypt. Open Access Maced J Med Sci 2019; 7:2189–2193.

4 Kovesdy CP, Furth. SL, Zoccali C. Obesity and kidney disease: hidden consequences of the epidemic. Braz J Med Biol Res 2017; 50:e6075.

5 Wahba IM, Mak RH. Obesity and obesity- initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol 2007; 2:550–562.

6 Martin-Taboada M, Vila-Bedmar R, Medina-Gomez G. From obesity to chronic kidney disease: how can adipose tissue affect renal function?. Nephron 2021; 145:609–613.

7 Lancha A, Frühbeck G, Gómez- Ambrosi J. Peripheral signalling involved in energy homeostasis control. Nutr Res Rev 2012; 25:223–248.

8 D' Amico G. Tubulointerstitium as predictor of progression of glomerular disease. Nephron 1999; 83:289–295.

9 Ucakturk A, Avci B, Genc G, Ozkaya O, Aydin M. Kidney injury molecule-1 and neutrophil gelatinase associated lipocalin in normoalbuminuric diabetic children. J Pediatr Endocrinol Metab 2016; 29:145–151.

10 Huang Y, Tian Y, Likhodil S, Randell E. Baseline urinary KIM-1 concentration in detecting acute kidney injury should be interpreted with patients pre- existing nephropathy. Pract Lab Med 2019; 15:e00118. DOI: 10.1016/j.plabm.2019.e00118

11 Gayret ÖB, Taşdemir M, Erol M, Nacaroglu HT, Zengi O, Yiğit Ö. Are there any new reliable markers to detect renal injury in obese children?. Ren Fail 2018; 40:416–422.

12 Dietitians of Canada. WHO growth charts for Canada, March 2014 revision. Available at: http://www.dietitians.ca/Dietitians-Views/Prenatal-and-Infant/WHO-Growth-Charts.aspx. [Accessed date 2014]

13 Joseph TF, David CK, Carissa MB-S., Douglas B, Aaron EC, Stephen RD, *et al.* Clinical practice guidelines for screening and management of high blood pressure in children and adolescents. Pediatrics 2017; 140: e20171904.

14 Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am 1987; 34:571–590.

15 Mathews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetolgoia 1985; 28:412–419.

16 Valerio G, Licenziati MR, Iannuzzi A, Franseze A, Siani P, Riccardi G, Rubba P. Insulin resistance and impaired glucose tolerance in obese children and adolescents from Southern Italy. Nutr Metab Cardiovasc Dis 2006; 16:279–284.

17 Ding W, Mak RH. Early markers of obesity – related renal injury in childhood. Pediatr Nephrol 2015; 30:1–4.

18 Wickman Ch, Kramer H. Obesity and kidney disease: potential mechanisms. Semin Nephrol 2013; 33:14–22.

19 Lee S, Bacha F, Arslanian SA. Waist circumference, blood pressure, and lipid components of the metabolic syndrome. J Pediatr 2006; 149:809–816.

20 Onat A, Avci GS, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. Int J Obes 2004; 28:1018–1025.

21 El-Shaheed AA. Blood pressure measurements in adolescents of different socioeconomic status. Sc J Az Med Fac (Girls) 2001; 22:1351–1364.

22 Goknar N, Oktem F, Ozgen IT, Torun E, Kuçukkoc M, Demir AD, Cesur Y. Determination of early urinary renal injury markers in obese children . Pediatr Nephrol 2015; 30:139–144.

23 Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res 2015; 116:991–1006.

24 Kotchen TA. Obesity-related hypertension: epidemiology, pathophysiology, and clinical management. Am J Hypertens 2010; 23:1170–1178.

25 Flynn J. The changing face of pediatric hypertension in the era of the childhood obesity epidemic. Pediatr Nephrol 2013; 28:1059–1066.

26 Bucher BS, Ferrarini A, Weber N, Bullo M, Bianchetti MG, Simonetti GD. Primary hypertension in childhood. Curr Hypertens Rep 2013; 15: 444–452.

27 Marko K, Viktor S, Kristina M, Velibor T, Zoran G. Metabolic profiles in obese children and adolescents with insulin resistance. Open Access Macedonian J Med Sci. 2018; 6:511–518.

28 Yoon YS, Park HS, Yun KE, Kim SB. Obesity and metabolic syndrome-related chronic kidney disease in non- diabetic, non-hypertensive adults. Metab Clin Exp 2009; 58:1737–1742.

29 Whaley-Connell A, Pavey BS, Afroze A, Bakrins GL. Obesity and insulin resistance as risk factors for chronic kidney disease. JCMS 2006; 1:209–214.

30 Polidori N, Giannini C, Salvatore R, Pelliccia P, Parisi A, Chiarelli F, Mohn A. Role of urinary NGAL and KIM-1 as biomarkers of early kidney injury in obese prepubertal children. J Pediatr Endocrinol Metab 2020; 33:1183–1189.

31 De Silva PMCS, Mohammed abdul KS, Eakanayake EM, Jayasinghe SS, Jayasumana C, Asanthi HB, *et al.* Urinary biomarkers KIM-1 and NGAL for detection of chronic kidney disease of uncertain etiology (CKDu) among agricultural communities in Sri Lanka. PLoS Negl – Trop Dis 2016; 10: e0004979.

32 Zhao X, Zhang Y, Li L, Mann D, Imig JD, Emmett N, *et al.* Glomerular expression of kidney injury molecule-1 and podocytopenia in diabetic glomerulopathy. AmJ Nephrol 2011; 34:268–280.

33 Myers BD, Chui F, Hilberman M, Michaels AS. Transtubular leakage of glomerular filtrate in human acute renal failure. Am J Physiol 1979; 237:319–325.

34 Fufaa GD, Weil EJ, Nelson RG, Hanson RL, Bonventre JV, Sabbisetti V, *et al.* Association of urinary KIM-1, L- FABP, NAG and NGAL with incident end- stage renal disease and mortality in American Indians with type 2 diabetes. Diabetologia 2015; 58:188–198.

35 Walkar SS, Sabbisetti V, Ämlöv J, Carlsson AC, Coresh J, Feldman HI, *et al.* Relationship of proximal tubular injury to chronic kidney disease as assessed by urinary kidney injury molecule-1 in five cohort studies. Nephrol Dial Transplant. 2016; 31:1460–1470.

36 Perco P, Oberbauer R. Kidney injury molecule-1 as a biomarker of acute kidney injury in renal transplant recipients. Nat Clin Pract Nephrol 2008; 4:362–363.

37 Nickolas TL, O' Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, *et al.* Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med 2008; 148: 810–819.

38 Humphreys BD, XU F, Sabbisetti V, Grgic I, Movahedi Naini S, Wang N, *et al.* Chronic epithelial kidney injury molecule-1 expression causes murine kidney fibrosis. J Clin Invest 2013; 123:4023–4035.

39 Edward N, Susan F, Bradley W, Mark M. Correlates of leptin in children with chronic kidney disease. J Pediatr 2014; 165:825–829.

40 Blüher M, Mantzoros CS. From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21St century. Metabolism 2015; 64:131–145.

41 Papafragkaki DK, Tolis G. Obesity and renal disease: A possible role of leptin. Hormones 2005; 4:90–95.

42 Zhu Q, Scherer PE. Immunologic and endocrine functions of adipose tissue: implications for kidney disease. Nat Rev Nephrol 2018; 14: 105–120.

43 Briffa JF, McAinch AJ, Poronnik P, Hryciw DH. Adipokines as a link between obesity and chronic kidney disease. Am J Physiol Renal Physiol 2013; 305:1629–1636.

44 Fakhrzadeh H, Ghodsi M, Hamidi A, Moayyeri A, Heshmat R, Poorebrahim R, *et al.* Relation between leptin and BMI and hypertension in obese children. Iran J Diabetes Lipid Disord 2005; 5:75–82.

45 Goswami B, Bhattacharjya H, Sengupta S, Bhattacharjee B. Associations of obesity and serum leptin level with elevated blood pressure among urban secondary school students of a northeastern city of India: A baseline observation. J Family Med Prim Care 2020; 9:1442–1447.

46 Daschner M, Tonshoff B, Blum WF, Englaro P, Wingen AM, Schaefer F, *et al.* Inappropriate elevation of serum leptin levels in children with chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. J Am Soc Nephrol 1998; 9:1074–1079.

47 Widecka J, Widecka-Ostrowska K, Ziemak J, Brzeska A, Glowala J, Miazgowski T, Widecka K. Comparison of the concentration of leptin between obese woman and obese men with essential hypertension. Arterial Hypertens 2016; 20:108–112.

48 Asayama K, Hayashibe H, Dobashi K, Uchida N, Nakane T, Kodera K, *et al.* Decrease in serum adiponectin level due to obesity and visceral fat accumulation in children. Obes Res 2003; 11:1072–1079.

49 Frithioff-Bøjsøe C, Lund MAV, Lausten-Thomsen U, Hedley PL, Pedersen O, Christiansen M, *et al.* Leptin, adiponectin and their ratio as markers of insulin resistance and cardiometabolic risk in childhood obesity. Pediatr Diabetes 2020; 21:194–202.

50 Sharma K, Ramachandrarao S, Qui G, Usui H, Zhu Y, Dunn S, *et al.* Adiponectin regulates albuminuria and podocyte function in mice. J Clin Invest 2008; 118:1645–1656.

51 Phillips SA, Giaraldi TP, Oh DK, Savu MK, Henry RR. Adiponectin secretion and response to pioglitazone is depot dependent in cultured human adipose tissue. Am J Physiol 2008; 295:E842– E850.

52 Declèves A, Mathew A, Cunard R, Sharma K. AMPK mediates the initiation of kidney disease induced by a high-fat diet. J Am Soc Nephrol 2011; 22:1846–1855.

53 Varda NM, Medved M, Ojstersek L. The associations between some biological markers, obesity, and cardiovascular risk in Slovenian children and adolescents. BMC Pediatr 2020; 20:81. DOI: 10.1186/s12887-020-1978-5

54 Tesauro M, Mascali A, Franzese O, Cipriani S, Cardillo C, Di Daniele N. Chronic kidney disease, obesity, and hypertension: the role of leptin and adiponectin. Int J Hypertens 2012; 2012:XX. (Article ID 943605). DOI: 10.1155/2012/943605

55 Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, *et al.* Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. J Clin Endocrinol Metab 2002; 87:5662–5667.

56 Mills KT, Hamm LL, Alper AB, Miller C, Hudaihed A, Balamuthusamy S, *et al.* Circulating adipocytokines and chronic kidney disease. PLoS ONE 2013; 8:e76902.

57 Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, *et al.* The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001; 7:941–946.

58 Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, Matsuzawa Y. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 2001; 50:1126–1133.