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Obesity induced renal injury: Could It be detected early?

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Abstract

Background: The onset of obesity-associated renal injury is insidious and asymptomatic. Therefore, finding an early marker will be extremely useful in its detection. Kidney injury molecule-1 (KIM-1) can be evaluated as an early marker for renal injury in obese children.

Methods: This case control study involved two groups: a case group of 45 Egyptian overweight/obese children and a control group of 45 non-obese peers. Anthropometry and blood pressure were measured in both groups. Additionally, KIM-1 and serum creatinine levels were assessed.

Results: Compared to the control group, the case group showed a significantly higher systolic (P-value 0.000) and diastolic (P-value = 0.002) blood pressure. A significantly higher serum creatinine (P=0.007) and KIM-1 (P=0.001) were also found.

Conclusion: It is inferred that obesity impacts renal hemodynamics early in childhood. Thus, identifying a screening marker like KIM-1 is useful for the early diagnosis of renal injury.

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Highlights

What is current knowledge?

Obesity leads to increased nephropathy risk and a significant rise in the incidence of chronic renal disease. Renal insult usually begins with an extra workload on glomerular filtration and damage to nephrons, resulting in injurious proteinuria, hypertrophy, and fibrosis. An elevated level of KIM-1 is present in the cellular damage of the proximal convoluted tubules.

What is new here?

KIM-1 may be used as a complementary method to detect or diagnose renal injury, with 88% sensitivity and 73% specificity.

Introduction

The predominance of obesity worldwide highlights its impact on increasing the risk of nephropathy in adulthood. Lately, and for the past 30 years, a higher prevalence of renal failure has gone hand in hand with an increase in the prevalence of high body mass index (BMI) (1,2,3). Obesity was also recognized for its powerful influence on acquiring a progressing renal insult. Fortunately, obesity is considered a risk that can be modified (4,5), and astonishingly, recent research has proven a similar phenomenon in childhood obesity. Obesity has potentiated the risks of nephropathy and has remarkably increased the incidence of chronic renal issues (6). The proposed renal pathological pathways in obese subjects are multiple and variable. An obesity-induced renal insult begins with an extra workload on glomerular filtration. The hyperfiltration nephrons are exposed to injurious proteinuria, hypertrophy, and fibrosis (7).

Currently, visceral fat is a well-recognized source of pro-inflammatory, hormonal, and oxidative stressors, which result in insulin resistance and predisposition to numerous metabolic diseases (8). Nowadays, many studies are directed to investigate the role of these stressors in targeting the kidneys and the potential glomerular damage caused by them. The chronic inflammatory milieu induced by obesity may be harmful to renal tissues and may trigger inflammation and fibrosis on a cellular level (9,10). In addition, the co-morbidities in association with obesity are injurious to the kidneys. The mostly encountered ones are systemic hypertension, insulin resistance, hypertriglyceridemia, hypercholesterolemia, sympathetic overactivity, imbalanced leptin/adiponectin hormones and other diseases that may cause a decline in kidney functions (3). The cells of the proximal convoluted tubules are the most sensitive to injury from the previously mentioned conditions (11).

Kidney injury molecule-1 (KIM-1) has been studied in both acutely and chronically injurious renal insults (12,13). KIM-1 is a type 1 cellular membranous glycoprotein (3,14). An elevated level of KIM-1 is always present in cellular damage of the proximal convoluted tubules (15,16). This injury marker has greatly served in assessing renal affection secondary to proteinuria, exposure to toxins, and/or ischemia (17,18).

The chief concern of the current research was to study the sensitivity and specificity of plasma KIM-1 as a screening tool for renal injury in overweight/obese adolescents.

Methods

Ethical approval was granted by the Ethical Committee of the National Research Centre before the start of the study. Written informed consent was signed by one of the parents on the behalf of each child in accordance with the code of ethics of the Declaration of Helsinki.

Ninety children and adolescents with the mean age 13.05 ± 2.61 years were enrolled in the study. The participants were stratified into two groups: Group 1 (Cases) with 45 Egyptian overweight/obese adolescents and Group 2 (Control) with 45 lean Egyptian adolescents. The participants were recruited from the Nutrition and Immunity Clinic at the Medical Research Centre of Excellence, the National Research Centre. The inclusion criteria were both sexes aged 10 to 18, and the exclusion criteria included syndromes of obesity and endocrinal causes of obesity.

Measurements were evaluated for each participant. The height was recorded to the nearest 0.5 cm on a Holtain portable anthropometer, and the weight was registered to the nearest 0.1 kg on a Seca scale balance with minimal clothes and without shoes. BMI was calculated as weight (kg)/height (m2).

Blood samples were collected from all 90 patients and centrifuged. Then, serum was isolated and stored at -20 until collection of all samples. Serum creatinine measurement was performed using a spectrophotometer, and KIM-1 was assessed using ELISA methods (Elabscience Biotechnology Co., Ltd, 1 Shzishanst, Wuhan, Hubei, China, 430070).

Descriptive data were presented as mean and standard deviation. Comparative data between the case and control groups were analyzed, and P-value was calculated. Results were considered significant at a P-value of $\leqslant 0.05$. Statistical analysis was performed using SPSS version 21.

Results

The groups were homogeneous in terms of age with an insignificant P-value of 0.446. As planned, the anthropometric measurements were significantly different between the cases and controls. A highly significant P-value of 0.001 was

observed for BMI scores between the cases and controls, as shown in Table 1.

Table 1. Descriptive data of studied groups

Parameter Mean ± SD	Overweight/obese n=45	Control n=45	p-value
Age	13.05 ± 2.61	12.62 ± 2.60	0.446
Weight	73.41 ± 18.26	37.39 ± 10.68	0.001*
Height	154.16 ± 10.65	146.05 ± 13.04	0.002*
BMI	30.55 ± 5.61	17.22 ± 2.71	0.001*
BMI percentile	98.30 ± 2.68	34.40 ± 28.16	0.001*

The complete blood count was comparable between the two groups. As shown in Table 2, highly significant P-values of 0.001 and 0.007 were obtained for KIM-1 and creatinine levels, respectively, in the cases compared to the controls.

Table 2. Laboratory investigations for studied groups

Parameter Mean ± SD	Overweight/obese BMI ≥ 85thpercentile n=45	Controls BMI < 85th percentile n=45	p-value
HGB	13.04 ±1.19	1.06±12.92	0.629
PLT	285.87±62.35	275.95±55.96	0.432
WBC	7.08±2.04	6.88±1.82	0.625
KIM-1ng/ml	4.49±1.30	2.42±1.39	0.001
Creatinine mg/dl	0.94±0.23	0.79±0.21	0.007

No correlations were found between KIM-1 and systolic and diastolic blood pressures in the case group, as shown in Table 3.

Table 3. Correlations between KIM-1, BMI, and systolic and diastolic blood pressures

Parameters	R (Pearson's Correlation Coefficient)	P-value	
KIM-1 with Systolic	0.160	0.324	Pa
KIM-1 with Diastolic	- 0.123	0.448	Nb

[a] Positive Correlation
[b] Negative Correlation

In our study, KIM-1 at a cutoff value of 3.00 was found to be a marker of high significance (P=0.001) for detection of early renal injury with a sensitivity of 88.4% and a specificity of 72.7%, as shown in Table 4 and Figure 1.

Table 4. Sensitivity and specificity of KIM-1 in case group

Parameter	AUC	Cut-off value	Sensitivity	Specificity	P-value	95% CI
Kim-1	0.856	3.000	88.4%	72.7%	0.001*	0.768 - 0.943

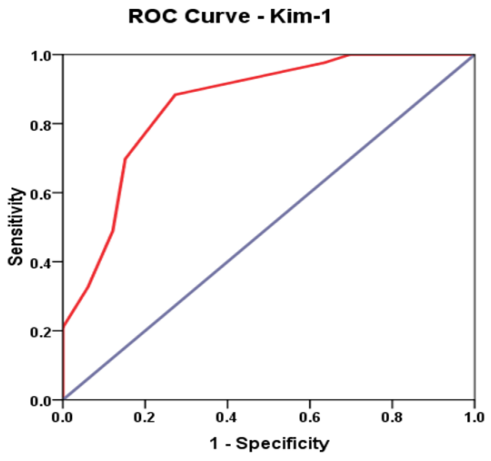

Figure 1. ROC curve for KIM-1 in case group

Discussion

Adolescence, according to the World Health Organization, is the stage of high vulnerability. Thus, we conducted the current study with special emphasis on this critical stage of life (19-25). To this end, 90 Egyptian adolescents were included in the study. The sex distribution was 58 females (64%) and 32 males (36%). The age ranged between 10-18 years. The participants were grouped according to BMI percentiles: a case group of 45 overweight/obese adolescents and a control group of 45 non-obese adolescents. A high BMI, defined as ⩾ 85th percentile, was used as the BMI cutoff point of risk criteria, through which the candidates were stratified into cases and controls. This "BMI-based selection" method was adopted by many authors (26-30). Nineteen out of 32 males (59%) were overweight/obese, compared to 26 out of 58 females (45%) who were overweight/obese.

As a strong point in our research, a highly significant discrepancy was observed in terms of BMI between the cases and controls. The reason is that it pronounced the impact of higher BMI on the obtained results. The P-value was 0.001 between both groups in terms of weight, BMI, and BMI percentiles.

We assessed blood pressure in all participants since hypertension is usually associated with obesity and is believed to impair renal function (31). This association was evident in our cases due to their significantly higher blood pressure compared to the controls. The P-values were 0.000 and 0.002 for measurements of systolic and diastolic pressures, respectively, reflecting the effect of high BMI on hemodynamics. Similarly, studies by Ding et al. and El-Shaheed et al. proved a positive correlation between BMI and both systolic and diastolic pressures among obese adolescents (32,33).

Also, the serum creatinine level was significantly higher in overweight/obese adolescents compared to their non-obese counterparts, with a P-value of 0.007. Although all of our cases had their creatinine levels within the normal range. This finding is in line with the result of a research by Van Dam et al., concluding that obesity negatively affects the creatinine level (34).

In many contemporary studies, KIM-1 has been considered a highly useful biomarker for acute and chronic renal injury (35-37). Urinary KIM-1 is a well-established marker of drug-induced nephrotoxicity, validated by the Food and Drug Administration since 2008 (38). The estimation of the KIM-1 level in blood is a new tool for renal injury assessment investigated in a multitude of recent studies (39,40). To the best of our knowledge, our study is the first to evaluate blood KIM-1 as a sensitive and specific marker of early renal injury in obese adolescents. A significantly higher KIM-1 value was found in the overweight/obese group (P-value=0.001). Blood KIM-1 was proven to have a sensitivity of 88.4% and a specificity of 72.7% at a 95% confidence interval. This is comparable to the findings of Sabbisetti et al., who assessed the sensitivity and specificity of KIM-1 through the ROC curve of blood KIM-1 in kidney injury associated with type 1 diabetes (40).

We did not find significant correlations between KIM-1 and blood pressure measurements in the case group. In contrast, Tomczak et al. found a significant positive correlation between KIM-1 and both systolic and diastolic readings (41).

Therefore, a scheduled routine monitoring of blood pressure measurements and the renal injury marker KIM-1 in overweight/obese children should be considered.

Conclusion

A significantly higher blood pressure was detected in overweight/obese cases compared to controls. A significantly higher KIM-1 value was found in the group of overweight/obese cases, denoting renal affection. With almost 88% sensitivity and 73% specificity, KIM-1 may be considered a complementary method alongside other diagnostic methods for detecting renal injury.

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Ethical statement

This research was performed in accordance with the code of ethics of the Declaration of Helsinki.

Conflicts of interest

None

Author contributions

Nermine N. conceived the idea, supervised each step in the research, and wrote most of the manuscript. Azza Abd El-Shaheed also contributed to the idea and supervised all phases of the research. Sara F., the corresponding author, collected data and contributed to manuscript writing. Rehab S. was responsible for data collection, resource management, and statistical analysis. Salwa R. and Hiba carried out most of the laboratory work. All authors reviewed and approved the final manuscript.

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