Cystatin and Glomerular Filtration Rate in Obese Versus Non-obese Adolescents

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Abstract

BACKGROUND: Obesity is well known as an independent risk factor for chronic kidney disease thus meticulous assessment of renal function is more essential in obese individuals. Glomerular filtration rate (GFR) is commonly estimated based on serum creatinine (Cr). However, using Cr as marker of kidney function has some limitations and cystatin C (CystC) has been reported as an alternative marker.

AIM: This study was designed to assess renal function using both GFR and cystatin in obese adolescents.

METHODS: This case-control study enrolled ninety Egyptian adolescents aged between 10 and 18-years-old who were divided equally into two groups according to body mass index (obese and non-obese). Each participant was subjected to full medical history taking, anthropometric measures, and laboratory investigation including Complete blood count, serum Cr, estimated GFR, and CystC.

RESULTS: Serum Cr level was significantly higher in obese adolescents compared to non-obese mean values of 0.94 and 0.79, respectively, with p = 0.007. Also, eGFR based on Cr was significantly lower in the obese group compared to controls 73.1 and 85.30, respectively with p = 0.048. CystC showed non-significant higher levels in obese group versus controls with mean value of 2.28 and 1.85, respectively with p = 0.928. CystC at cut-off value of 1.525 and 95% CI showed a sensitivity of 47.2% and specificity of 63.9% for evaluation of kidney affection in obese children and adolescences.

CONCLUSION: GFR is affected in obese adolescence with elevation of serum Cr and unexpected non-significant elevation of CystC in obese adolescence when compared by the control group.

Introduction

Childhood obesity became an epidemic problem in both developed and developing countries. It is known to have a significant impact on both physical and psychological health [1]. Furthermore, an emergent interest in the link between obesity and renal injury has been existed. A high body mass index (BMI) is strongly related to new-onset chronic kidney disease (CKD) since a compensatory hyperfiltration occurs according to the higher metabolic demand of the increased body weight (WT). This augmented intraglomerular pressure may enhance kidney damage and, in the long term, raise the risk for CKD. Obesity is also suggested to be a risk factor for nephrolithiasis, and kidney cancer [2]. The renal effect of pediatric obesity has not been adequately investigated besides the incomplete consensus on the various parameters of renal function [3].

In early kidney injury, serum creatinine (Cr) does not increase until moderate reduction in GFR occurs [4].

Cystatin C (CystC) is a 122-amino acid basic protein that synthesized by nucleated cells and freely filtered through the glomeruli. It is reabsorbed and totally metabolized in kidney tubular cells without excretion, so it can be an alternate marker for GFR [4].

Moreover, serum CystC is not affected by age, gender, race, and muscle mass and also does not have a lag period for rising in early kidney injury [5], [6].

Thus this study was conducted to assess renal function in obese Egyptian adolescents using GFR, Cr, and cystatin and try to find the best method for detecting early kidney affection.

Subjects and Methods

This case-control study was conducted at the Medical Research Centre of Excellence in the clinic of immune-nutrition, in the National Research Centre.

Ninety Egyptian adolescents who aged between 10 and 18-years-old were selected on purpose of BMI in this study and divided into two groups according to BMI. Obese group included forty-five children with BMI ≥85th centile while the control group enrolled forty-five matched peers with BMI <85th centile. Children with syndromic and endocrinal causes of obesity were excluded from this study. Approval of the study protocol was obtained by the Ethical Committee of the Egyptian National Research Centre No 16130. Before the study, each participant's legal guardian signed a written informed consent form in accordance with the World Medical Association's code of ethics (Helsinki Declaration) [7].

Each participant was subjected to

1. Full medical history taking including family history of obesity and other health problems.
2. Anthropometric measures including height (HT) that determined to the nearest 0.5 cm on a Holtain portable anthropometer (University of London Institute of Child Health), and WT which measured to the nearest 0.1 kg on a Seca scale Balance (Model 767 1321004), made in Germany with the child dressed in minimal clothing and no shoes. BMI was also calculated as WT (kg)/HT (m^2). Data were then plotted on the WHO curves using the software AnthroCalc v1.66 Homeon WHO curves [8].
3. Laboratory investigation including complete blood count, serum Cr, estimated GFR (eGFR)= 0.413*(HT/Standardized Serum Cr) and cystatin. Human CystC ELISA Kit Cayman chemical, USA was used for the quantitative determination of serum CystC concentration that is produced by Sino Gene Clon Biotech Co., Ltd, catalog No. SG 10555.

Statistical analysis

Data analysis was performed using Statistical Package for the Social Science (SPSS) version 21 (SSPS Inc, Pennsylvania, USA). Continuous data were expressed as mean ± SD, non-parametric data presented as median and range while categorical data were expressed as frequencies and percentages. Categorical variables were compared using Chi square analysis while continuous non-parametric variables were compared by the Mann-Whitney test. Independent t-test was used also for the comparison between two groups with quantitative parametric data. p-value was considered statistically significant at p < 0.05. The sensitivity and specificity of cystatin for the detection of kidney affection in obese children were assessed by the receiver operating characteristic (ROC) curve.

Results

The current study enrolled two groups of obese and non-obese children who aged 13.05 ± 2.61 and 12.62 ± 2.60 respectively with non-significant difference between both groups (p = 0.446). Female sex was more predominant in both groups (71.1% in obese, 60% in non-obese) with non-significant difference (p = 0.267) (Table 1).

Table 1: Demographic and anthropometric data of the studied groups

Parameters	BMI Centile	Min.	Max.	Mean ± SD	p value
Age[a]	Obese	9.00	18.00	13.05 ± 2.61	0.446
	Non-Obese	8.00	17.00	12.62 ± 2.60	
Sex*	Male	13 (28.9%)	18 (40%)	1.230*	0.267
	Female	32 (71.1%)	27 (60%)		
WT[a] (kg)	Obese	38.50	128.50	73.41 ± 18.26	0.001
	Non-Obese	18.00	66.00	37.39 ± 10.68	
WT SD[b]	Obese	0.96	3.00	2.18 ± 0.69	0.001
	Non-Obese	−4.06	0.86	−1.01 ± 1.21	
WT Centile[b]	Obese	83.00	99.90	96.26 ± 4.80	0.001
	Non-Obese	0.10	80.80	27.43 ± 25.05	
HT[a] (cm)	Obese	131.50	175.00	154.16 ± 10.65	0.002
	Non-Obese	114.50	171.50	146.05 ± 13.04	
HT SD[b]	Obese	−2.54	2.32	0.26 ± 1.07	0.001
	Non-Obese	−3.93	1.19	−0.83 ± 1.23	
HT Centile[b]	Obese	0.60	98.20	51.50 ± 28.89	0.003
	Non-Obese	0.10	88.00	32.60 ± 28.74	
BMI[a]	Obese	20.00	42.90	30.55 ± 5.61	0.001
	Non-Obese	12.20	25.10	17.22 ± 2.71	
BMI SD[b]	Obese	1.25	3.00	2.47 ± 0.57	0.001
	Non-Obese	−3.00	0.94	−0.72 ± 1.15	
BMI Centile[b]	Obese	89.60	99.90	98.30 ± 2.68	0.001
	Non-Obese	0.10	82.90	34.40 ± 28.16	

[a]Comparison between the groups using independent samples t-test at sig. level 0.05 (Parametric data), [b]Comparison between the groups using Mann-Whitney test at sig. level 0.05 (Non-Parametric data), *Chi-Square. WT: Weight, HT: Height, BMI: Body mass index.

Regarding BMI of both groups, its mean was 30.55 ± 5.61 in the obese group and 17.22 ± 2.71 in the non-obese group with a significant P value of 0.001. There was also significant difference between both groups regarding, WT, WT standard deviation, WT centile, BMI SD, and BMI centile (p = 0.001). Furthermore, there were significant differences between both groups regarding HT, HT SD, HT centile (P = 0.002, 0.001, and 0.003, respectively) (Table 1). Cystatin levels in obese group showed insignificant higher values (2.28 ± 2.55) compared to non-obese group (1.85 ± 0.64) with p = 0.928 (Table 1).

Concerning laboratory findings, there was not significant difference between the two groups regarding hemoglobin, platelet count, and white blood cell count (p = 0.629, 0.432, 0.625, respectively) (Table 2).

Table 2: Laboratory data of the studied groups

Parameters	BMI Centile	Mean ± SD	p value
Hemoglobin[a] (g/dl)	Obese	13.04 ± 1.19	0.629
	Non-Obese	12.92 ± 1.06	
Platelet count[a] (thousands/cmm)	Obese	285.87 ± 62.35	0.432
	Non-Obese	275.95 ± 55.96	
White blood cell[a] (thousands/cmm)	Obese	7.08 ± 2.04	0.625
	Non-Obese	6.88 ± 1.82	
Cystatin[b] (mg/L)	Obese	2.28 ± 2.55	0.928
	Non-Obese	1.85 ± 0.64	
Creatinine[a] (mg/dl)	Obese	0.94 ± 0.23	0.007
	Non-Obese	0.79 ± 0.21	
GFR[b]	obese	73.10 ± 22.33	0.048
	Non-Obese	85.30 ± 32.25	

[a]Comparison between the groups using Independent Samples T-Test at sig. level 0.05 (Parametric data), [b]Comparison between the groups using Mann-Whitney Test at sig. level 0.05 (Non-Parametric data). GFR: Glomerular filtration rate, BMI: Body mass index.

Regarding Cr levels, it was significantly higher in obese children (0.94 ± 0.23) compared to non-obese

(0.79 ± 0.21) with p = 0.007, (Table 2). The eGFR using Cr level was also significantly lower in obese children (73.10 ± 22.33) compared to non-obese (85.30 ± 32.25) with p = 0.048 (Table 2).

Table 3: Medical history of the studied groups

Parameters	Groups	BMI centile		Chi-square	p value
		Obese N (%)	Non-Obese N (%)		
Obese Family Member	Yes	36 (81.8)	26 (59.1)	5.459	0.019
	No	8 (18.2)	18 (40.9)		
Renal Disease of a Family Member	Yes	13 (29.5)	10 (22.7)	0.530	0.467
	No	31 (70.5)	34 (77.3)		
Diabetes Mellitus in the Family	Yes	31 (70.5)	31 (70.5)	0.001	1.000
	No	13 (29.5)	13 (29.5)		
Hypertension in the Family	Yes	18 (40.9)	25 (56.8)	2.228	0.135
	No	26 (59.1)	19 (43.2)		
Dyslipidemia in the Family	Yes	4 (9.1)	6 (13.6)	0.451	0.502

When it comes to family history, 36 (81.8%) of obese group had an obese family member compared to 26 (59.1%) of the non-obese group with a significant difference (p = 0.019). However, there was no significant difference between both groups regarding other parameters of family history including renal disease, diabetes mellitus, hypertension, and dyslipidemia (p = 0.467, 1.000, 0.135, and 0.502, respectively) (Table 3) ROC curve at 95% CI of cystatin for the detection of kidney affection in obese children showed sensitivity of 47.2 % and specificity of 63.9 % (Table 4 and Figure 1).

Table 4: ROC curve for obese group in the following parameters

Parameters	AUC	Cut-off value	Sensitivity %	Specificity %	p-value	95% CI
Cystatin	0.506	1.525	47.2	63.9	0.928	0.371–0.642

ROC: Receiver operating characteristic.

Discussion

Obesity is known as a risk factor for the progression of kidney disease. It may also increase mortality risk among children with end-stage renal disease (ESRD). Later in life, healthy overweight and obese children have a higher risk of all-cause ESRD [9]. Thus early evaluation of renal function in obese children is highly important. So, this study was conducted on obese children aged between 10 and 18-years-old to study kidney condition among them and to detect the reliable biomarker for early kidney assessment.

The results showed that serum Cr was significantly higher in obese participants compared to control besides significant lower e GFR based on Cr. Salman *et al.*, also reported significant lower cr-based eGFR in obese children compared to controls [10]. Correia-Costa *et al.*, evaluated 150 overweight/obese children and showed that overweight/obese children had lower eGFR compared to controls, using numerous formulae [3]. Miliku *et al.*, reported that both eGFR-Cr and eGFR-cystC can be influenced by BMI and body surface area with more influence of eGFR-Cr by body composition [11]. Furthermore, the study of Cindik *et al.*,
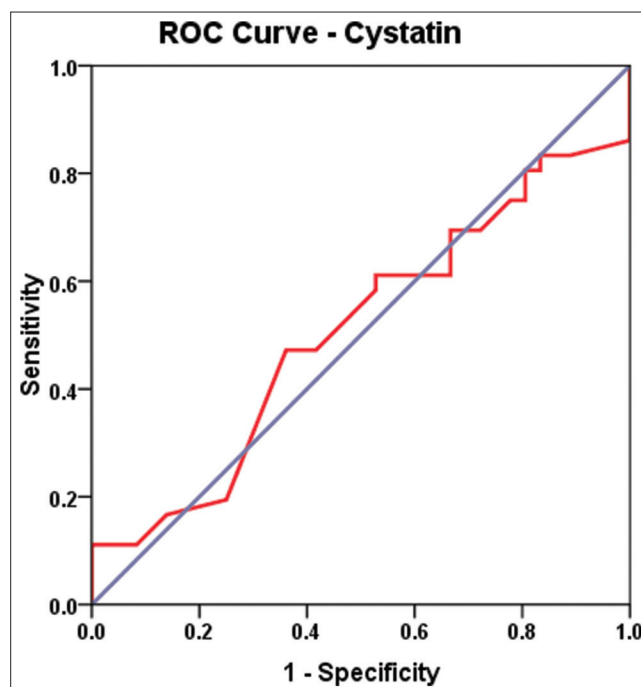

Figure 1: ROC curve for obese group regarding cystatin level. ROC: Receiver operating characteristic

on children aged 7–16.5 years; showed a significant positive correlation between GFR and BMI [12].

For CystC, the current study showed non-significant elevation in obese group compared to control. Salman *et al.*, similarly detect non-significant difference between obese children and control besides significant higher mean CystC levels in obese group with metabolic syndrome compared to non- metabolic syndrome group [10]. Actually, Muntner *et al.*, and Shankar *et al.*, reported a graded association between higher BMI and higher CystC in adults, this may explain the importance of WT and BMI monitoring in obese children and adolescence to avoid its dangerous sequels in adulthood life [13], [14]. El-Shaheed *et al.*, conclude that physical activity was encountered in obese adolescence than non-obese one through a WHO validated questionnaire and recommends to raise the awareness and importance to enhance physical activity in obese adolescence to avoid its future complications [15].

Another research found that the most powerful influencers on eating behaviors in adolescence are media, friends and family. Thus, good parental support and understanding have a major imprint on reforming such harmful effect of faulty eating habits. Also, scholastic and college healthy eating programs are extremely important as a source of easy access to widespread information, in order to reduce risk of obesity in this age group [16]. In the current study, the sensitivity and specificity of cystatin for the detection of kidney affection in obese children was 47.2% and 63.9% respectively. Higher sensitivity (81%) and specificity (88%) for CystC compared to Cr for estimating renal function in children and adults was reported in the meta-analysis of Roos

et al. [17]. Hojs *et al*., also reported that CystC-based eGFR equation is more sensitive, specific and accurate in overweight and obese persons compared to that of Cr-based eGFR [18]. In the study of Narvaez-Sanchez *et al*., diagnostic accuracy of CystC and Cr for estimating GFR was calculated in children with suspected or definite renal insufficiency and aged <18 years. Their results showed CystC sensitivity 75%, specificity 84%, and SCr sensitivity 46%, specificity 100% by using a cut-off value of GFR at 90 mL/min. They concluded that CystC can replace serum Cr for evaluating and monitoring kidney function in children [19].

Finally and from the above results, it is now obvious that obesity can unfavorably affect kidney function. Early and precise evaluation can be assessed by Cr and GFR as a sensitive biomarker for kidney affection in obese children. However, this study has some limitations including small sample size and incomplete evaluation of renal function by other parameters. So in the future, the research on a comprehensive follow-up study will express the importance of Cystatin in the follow-up of obese children and adolescence together with relation to BMI.

Conclusion

GFR is affected in obese children. Elevated serum Cr andfollow-up of serum CystC will be needed in obese children and adolescence Thus, Cr used as a marker for kidney affection in obese children.

Acknowledgment

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