ORIGINAL ARTICLE

Kidney function in obese adolescents with or without metabolic syndrome in a nationally-representative sample of pediatric population: First report from the Middle East and North Africa: The CASPIAN-III Study: A Case-Control Study

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Background: Obesity in accordance with metabolic syndrome (MetS) confronts populations at the higher risk of morbidity and mortality of chronic diseases including, chronic kidney diseases (CKD). The renal complication of obesity and MetS has been less debated in young adolescents. The objective of this study was to assess the kidney function in obese adolescents with or without MetS. **Materials and Methods:** The data used in this study were collected as part of a national study entitled Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable disease Study. The present study was conducted on a sub-sample of 113 obese adolescents (body mass index >95th percentile) aged between 10 years and 16 years selected by convenient sampling from the whole population studied. Anthropometric indexes and blood pressure were examined. A 12-h fasting serum was obtained for each participant to measure blood glucose, lipid profile, quantitative C-reactive protein (hs-CRP), Cystatin-c, urea, and creatinine. Fasting spot urine was collected to determine microalbumin and creatinine. Based on the study findings, participants were assigned into two groups with and without MetS. **Results:** The mean of microalbuminuria was in similar ranges in two groups and while the mean glomerular filtration rate (GFR) calculated by Bokenkamp's, updated and combined Schwartz's formulas were significantly lower in MetS + obese group in comparison with obese group. The similar result was not achieved by Filler's formula. Among MetS components, waist circumference had a correlation with hs-CRP ($P = 0.04$; $r = 0.15$). GFR was calculated based on the Schwartz formula and Cystatin-c formulas had no significant correlation with any MetS components. **Conclusion:** Our findings suggest that MetS can increase the risk of kidney dysfunction in obese adolescents. More studies are suggested in this regard in the pediatric population.

Key words: Kidney function, obesity, pediatric metabolic syndrome

INTRODUCTION

According to the World Health Organization (WHO), non-communicable diseases (NCDs) will be the cause of 75% of death by the year 2020.[1] The prevalence of obesity and metabolic syndrome (MetS), as pre-disposing factors of NCDs, is growing up worldwide.[2-6] Obesity and MetS are considerably prevalent among children and adolescents, and are no more limited to high-income countries.[7]

The prevalence of MetS is considerably high in Iranian children and adolescents.[4,8]

The role of obesity in inducing, endothelial dysfunction and cardiovascular complications has been widely accepted.[3,9-12] The higher likelihood of MetS has been reported in children with combined central and generalized obesity than in those with isolated generalized obesity.[13] Indeed obesity in accordance with MetS confronts populations at the higher-risk of morbidity and mortality such as atherosclerosis, cardiovascular accidents, and chronic kidney diseases (CKD).[3,14-21] CKD should be defined as the presence of kidney damage and the decrease in the level of kidney function based on the glomerular filtration rate (GFR).[22] The renal complications of obesity and MetS has less been debated in young adolescents and the objective of this study was to assess renal function in obese adolescents with or without MetS.

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Received: 30-11-2012; **Revised:** 03-02-2013; **Accepted:** 04-02-2013

MATERIALS AND METHODS

The data used in this study were collected as a part of the national survey of school student high-risk behaviors (2009-2010) as the third survey of the school-based surveillance system entitled Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable disease (CASPIAN-III) Study. This school-based nationwide health survey was conducted among 5570 students living in urban and rural areas of 27 provinces in Iran. Participants were recruited by multistage random cluster sampling from urban and rural areas of 27 provincial counties in Iran.[23] The present study was conducted on a sub-sample of 113 obese adolescents aged between 10 years and 16 years selected by convenient sampling from the whole population studied.

The survey was performed in accordance with the ethical standards of the Helsinki Declaration. The main study approved by the institutional review boards at national and provincial level and the current sub-study was approved by the Ethics Committee of the Research Department of Isfahan University of Medical Sciences.

After complete explanation of the study objectives and protocols for students and their parents, written informed consent was obtained from parents and oral assent from students.

A team of trained health-care professionals recorded information in a checklist and carried out the examinations under standard protocol by using calibrated instruments. Based on standard protocol, weight, height, and waist circumference (WC) were measured, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Weight was measured to the nearest 200 g in barefoot and lightly dressed condition. WC was measured to the nearest 0.5 cm at the end of expiration at the midpoint between the top of iliac crest and the lowest rib in standing position. WC and height were measured using a non-elastic tape and the blood pressure was assessed by using mercury sphygmomanometer in 3 consecutive measurements.

We used the WHO growth curves to define BMI categories, i.e., underweight as sex-specific BMI<-2 z-score, overweight as sex-specific BMI for age of >+1 z-score, and obesity as sex-specific BMI for >+2 z-score.[24]

To describe MetS, adjusted criteria for age, sex, and ethnicity described by Weiss *et al*.[5] were used with the following criteria:

Obesity was defined based on a threshold BMI adjusted for age and sex, z score of 2 or more. High-systolic or diastolic blood pressure was interpreted as having 3 measurements above 95th percentile for age, sex, and height. The results for triglycerides and high-density lipoprotein (HDL) were considered as age-and sex-specific percentiles, i.e., >95th percentile for triglycerides and <5th percentile for HDL cholesterol.[9] Impaired glucose tolerance was considered as a fasting blood glucose level greater than 100 mg per deciliter.

A 12-h fasting serum was obtained for each participant to measure blood glucose, lipid profile, quantitative CRP (hs-CRP), Cystatin-c, urea, and creatinine. Fasting spot urine was collected to determine microalbumin and creatinine. Microalbumin was assessed on fasting urine samples by Nephelometry (turbidometry) method, Pars-Azmoon kit number 2055015, Iran. Urine microalbumin/creatinine ratio more than 30 was considered abnormally high.[25] Serum creatinine, quantitative CRP, lipid profile, and blood urea nitrogen (BUN) were measured enzymatically on a Hitachi 7350 auto analyzer. Serum Cystatin-c was measured by particle-enhanced immunoturbidimetric method (Dako, Denmark). To calculate GFR 4 different formulas were applied[26-29] and among those formulas that calculated GFR based on Cystatin-c, the method of measuring Cystatin-c in combined Schwartz formula and Bokenkamp *et al*. formula were similar to our study.

1-Up-dated Schwartz formula[26] that calculates GFR based on serum creatinine and height:

GFR = K. height (cm)/Serum creatinine (mg/dl)

K for female 10-16 years = 0.55

K for male 10-16 years = 0.7

2-Combined Schwartz formula [26] that calculates GFR based on serum Cystatin-c, creatinine and height:[27]

GFR = 39.1 × [height (m)/creatinine] 0.516 × [1.8/Cystatin-C] 0.294 × [30/BUN] 0.169 × [height (m)/1.4] 0.188 × 1.099 (if male)

3-Cystatin-C based formula adapted from Bo¨kenkamp *et al*.[28]

GFR = (162/Cystatin-c)-30

4-Cystatin-C based formula adapted from Filler *et al*.:[29]

log GFR = 1.962 + 1.123 × log (1/Cystatin-C)

Whether the participants met three or more of the above mentioned criteria, they were assigned into obese group without MetS (group 1) or obese + MetS group (group 2).

Seventy out of 113 participants had the criteria of group 1 and the remaining met the criteria for group 2.

Microalbuminuria was measured in two fasting urine samples with a sampling interval of at least 1-2 month.[25]

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) software package version 16.0 (SPSS Inc., Chicago, IL, USA). The categorized data are reported as frequencies, percentages. Continuous data are reported as the mean and standard deviation (SD). Pearson's correlation test was used to analyze correlations. *P* value of less than 0.05 was considered as significant.

RESULTS

Seventy out of 113 participants were in group 1 (obesity without MetS) and 43 in group 2 (obese + MetS). As presented in Table 1, the mean age was not significantly different between groups, 12.1 ± 1.5 years versus 11.8 ± 1.7 years in group 1 and 2 respectively; $P > 0.05$. The male/female ratio did not differ significantly between groups, $P > 0.05$. Although, the percentage of microalbuminuria was higher in group 2 (83.7%) comparing with group 1 (74.3%), but it was not statistically significant. Participants with MetS and obesity had significantly higher WC than obese participants, $P = 0.02$. However, BMI was in the same range in both groups. Means of systolic and diastolic blood pressure measurements were not significantly different between groups and the values of hS-CRP were significantly higher in obese + MetS group (group 2) compare with obese group (group 1). The mean of microalbuminuria was in similar ranges in two groups [Table 2]. While mean GFR calculated by Bokenkamp's, up-dated and combined Schwartz's formulas were significantly ($P < 0.05$) lower in MetS + obese group (group 2) in comparison with group 1, the similar result was not achieved by Filler's formula; Table 2. Among MetS components, WC had a correlation with hs-CRP ($P = 0.04$; $r = 0.15$). However, WC had a strong inverse correlation with HDL levels ($P < 0.0001$; $r = –0.599$). In addition, HDL had reverse correlation with the following parameters: Fasting blood sugar ($P < 0.0001$, $r = –0.492$), triglyceride levels ($P < 0.001$, $r = –0.296$), and hs-CRP ($P = 0.001$, r = –0.302). Triglycerides levels had positive correlation with both hs-CRP ($P = 0.04$, $r = 0.161$) and fasting blood sugar (FBS) ($P = 0.001$, $r = 0.299$). GFR calculated based on the Schwartz formula[26] and Cystatin-c formulas[27-29] had no significant correlation with any MetS components, Table 3.

DISCUSSION

In this study, we evaluated different aspects of kidney function in obese adolescents with and without MetS. To the best of our knowledge, this study is the first of its kind in the pediatric age group. We observed that some aspects of kidney function deteriorated in obese adolescents with MetS in comparison with those without MetS.

Obesity and insulin resistance have been introduced as risk-factors for evolving MetS even in children.[30,31] There is growing body of evidence regarding the contribution of obesity and MetS to CKD in adult Participants.[14-16,32,33] A cohort study on 10096 adults at the risk of atherosclerosis revealed that approximately 7% of the participants with MetS developed CKD (odds ratio = 1.43).[20] Chen *et al.*

Table 1: Characteristics of the study participants

Parameters	Mets+obese group mean±SD *n*=43	Obese group mean±SD *n*=70	*P* value
Age (year)	11.8±1.7	12.1±1.5	0.4
Male/Female ratio	1.38	1.30	0.12
Waist circumference (cm)	78.14±11.5	73.2±11.7	0.023
Weight (kg)	56.4±10.2	56.7±9	0.87
Height (cm)	150.3±7.7	153.6±9.5	0.06
BMI (Kg/m^2)	25±4.6	24.2±4.2	0.33
BMI (Z-Score)	1.43±0.81	1.31±1.17	0.53
High density lipoprotein-cholesterol (mg/dl)	44±7.8	47.2±7.7	0.035
Triglycerides (mg/dl)	106.6±51.6	94±28.7	0.092
Blood glucose (mg/dl)	96.5±12.9	94.7±12.3	0.48
Systolic blood pressure (mmHg)	114±5	116±7	0.2
Diastolic blood pressure (mmHg)	70.9±2.9	71.2±3.2	0.64

BMI= Body mass index

Table 2: Markers of kidney function in obese children with or without metabolic syndrome

Parameters	Mets+obese group Mean±SD	Obese group Mean±SD	Significance
Serum creatinine (mg/dl)	0.89±0.1	0.78±0.1	0.001
Serum cystatin-C (mg/l)	0.87±0.14	0.81±0.1	0.01
Microalbumin/ Creatinine (mg/gm)	15.8±2.4	15.9±4.9	0.59
hs-CRP (mg/l)	1.2±1	0.95±0.19	0.048
GFR (Schwartz formula)[26]	105±20.1	127.9±24.9	0.001
GFR (Combined Schwartz formula)[27]	71.03±6.41	78.91±6.93	0.0001
GFR (Bo¨Kenkamp's formula)[28]	160.9±31	172.8±23.4	0.02
GFR (Filler's formula) [29]	116.9±17.09	118.07±21.07	0.7

GFR= Glomerular filtratin rates; hs-CRP= High sensitive-C reactive protien

Table 3: The correlation among glomerular filtratin rate and metabolic syndrome measures

Variables	Waist	HDL	FBS	GFR.cr	GFR.cystatin
Waist					
Pearson correlation	1	0.116	−0.064	−0.138	−0.062
Sig. (1-tailed)	-	0.111	0.249	0.073	0.258
HDL					
Pearson correlation	0.116	1	−0.492**	0.035	−0.043
Sig. (1-tailed)	0.111	-	<0.0001	0.355	0.324
FBS					
Pearson correlation	−0.064	−0.492**	1	0.032	−0.059
Sig. (1-tailed)	0.249	<0.0001	-	0.366	0.267
GFR.cr					
Pearson correlation	−0.138	0.035	0.032	1	0.066
Sig. (1-tailed)	0.073	0.355	0.366	-	0.245
GFR.cystatin					
Pearson correlation	−0.062	−0.043	−0.059	0.066	1
Sig. (1-tailed)	0.258	0.324	0.267	0.245	-

HDL= High-density lipoprotein; GFR=Glomerular filtratin rate; FBS=Fasting blood sugar; **= P<0.05

showed an odds ratio of 1.64 for CKD and elevated serum creatinine in participants with MetS compared to those without.[34] A follow-up of 1440 Japanese adult participants demonstrated that 10.6% of those with MetS developed CKD after 5 year follow-up.[35]

Tubular hyper-reabsorption, pressure natriuresis, renal vasodilatation, increased intra-glomerular hydrostatic pressure, and rising GFR are known major hemodynamic disturbances that are responsible for kidney impairment in obesity.[36] The main histopathologic feature of obesity-related glomerulopathy is glomerular sclerosis (GS), caused by glomerular hyper filtration and hypertrophy.[17-19,33] Obviously, microalbuminuria and subsequently overt proteinuria are the consequences of GS.[21,22] Indeed, the MetS has been introduced as an independent risk-factor for CKD with increasing the chance of CKD along by increasing the number of MetS traits.[20,35] Whether renal function impairment is a result of MetS or prolonged hypertension and hyperglycaemia, remained to be determined.[37,38] Since we selected Participants in both groups with similar range of height, weight, and BMI to diminish the chance of interfering confounding variables, mean of serum creatinine was significantly lower in obese adolescents without MetS. Consequently, GFR based Schwartz formula was considerably higher in this group.

In obese adolescents (group 1), GFR values calculated by Bokenkamp's, up-dated and combined Schwartz formulas showed higher amounts in compared with group 2. We did not observe the significant difference when we applied Filler's formula. This discrepancy among three Cystatin-c based formulas may be explained by the methods of measuring Cystatin-c. We used particle-enhanced immunoturbidimetric method to measure Cystatin-c, a method by which Bokenkamp's and Schwartz formulas had been developed. Filler *et al*. applied enzyme-linked immunosorbent *assay* (ELISA) method in this regard. Therefore, when using Filler's method, it is better to put the amounts of Cystatin-c measured by ELISA method. De Boer *et al*. found that WC, baseline BMI and fat mass were associated with faster loss of estimated GFR (calculated by MDRD Study equation) in obese adults. Nevertheless, the GFR based on the Cystatin-C formula had no association with obesity measures.[39] Similarly, we did not found any association among MetS traits and GFRs based on Schwartz and Cystatin-C formulas.

The increased GFR in obese may be a result of increased transcapillary hydraulic pressure difference.[18] Although, our Participants had high-normal blood pressure in comparison with normal population (data not shown), we did not demonstrate a significant high-blood pressure among obese Participants. However, the longer follow-up may reveal hypertension in obese adolescents. Obesity has been known as a cause of essential hypertension. The exact mechanisms of hypertension in obesity are not fully understood and it has been introduced that abnormal kidney function may contribute to provoke hypertension in obesity.[36] However, in our study a significant difference in blood pressure between obese Participants with and without MetS was not achieved. Although, we did not observed higher blood pressure and/or blood glucose levels in MetS group, this group showed renal dysfunction. Hypertension has been widely accepted as a major cause of chronic kidney disease in obesity and MetS.[40-42] However, our Participants who had lower GFR (obesity + MetS) did not have higher blood pressure. Severe obesity has been introduced to have a link with hypertension, decreased GFR and microalbuminuria.[43-48] Nevertheless, severe obesity was not a frequent finding among our participants. Ramkumar *et al*. demonstrated a strong correlation between hs-CRP level, high-BMI and CKD in obese Participants.[49] We did not achieve the same result in our study. No MetS trait had correlation with calculated GFRs in our Participants.

Among MetS traits, two of them were significantly different between groups: WC and serum HDL level. WC, as an independent risk-factor for MetS, was higher in group 2 than obese group 1. The study by Flodmark *et al*. on 29 obese adolescents revealed that WC had reverse correlation with HDL levels.[50] The same result was achieved by our study; r = –0.599, P = 0.0001. Hirschler *et al*. reported that WC was a predictor of insulin resistance in obese children to identify children at risk of MetS.[51] Further, the degree of insulin resistance affected the rate of comorbidities in obese

adolescents.[52] The serum insulin level was not measured in our study. We demonstrated an inverse correlation between FBS and HDL level and positive correlation between FBS and triglyceride levels. However, the level of fasting blood glucose was not significantly different between groups.

The lower age of our participants may explain the difference between our results and other studies. The limitation of our study was the shortage of the eligible participants. Longitudinal studies on children and adolescents are required to describe the effects of MetS and obesity on kidney function in youth.

Study limitations and strengths: The main limitation of this study is its cross-sectional nature. The main strengths of the study are its novelty in the pediatric age group, and including a nationally representative of population-based participants.

CONCLUSION

We concluded that MetS is associated with increased risk of kidney dysfunction in obese adolescents. The obese adolescents and children should be assessed regularly for kidney function. The clinical impact of our findings should be determined in future longitudinal studies.

ACKNOWLEDGMENTS

This school-based nationwide health survey was conducted in Iran with corporation of the Ministry of Health and Medical Education, Ministry of Education and Training, Child Growth and Development Research Center, Isfahan University of Medical Sciences, and Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences in Iran. This sub-study was conducted as a thesis funded by Isfahan University of Medical Sciences.

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How to cite this article: Kelishadi R, Gheissari A, Bazookar N, Motlagh ME, Taslimi M, Ardalan G. Kidney function in obese adolescents with or without metabolic syndrome in a nationally-representative sample of pediatric population: First report from the Middle East and North Africa: The CASPIAN-III Study: A Case-Control Study. J Res Med Sci 2013;18:178-83.

Source of Support: This work was conducted as a thesis funded by Isfahan University of Medical Sciences. It was conducted as a sub study of the national study (CASPIAN III), **Conflict of Interest:** None declared.