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Evaluation of Renal Function in Obese Children and Adolescents Based on Serum Cystatin C, Estimated Glomerular Filtration Rate Formulas, and Proteinuria: Which is Most Useful?

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What is already known on this topic?
The effects of obesity and metabolic syndrome on kidney function in the children and adolescent age group have not been adequately examined. There is insufficient data on the degree of impairment of renal function and the clinical significance. There is also no consensus on which of the parameters that assess renal function is reliable and reflects true renal function.

What this study adds?
Cystatin C could be used as an earlier biomarker than creatinine in the detection of impaired renal function in obese children, especially those with metabolic syndrome. Creatinine based formulas represent hyperfiltration as the first difference in renal function. Decreasing estimated glomerular filtration rate seen with cystatin C-based formulas in metabolic syndrome patients may represent the early stages of renal damage. Using fat free mass or body cell mass for estimated glomerular filtration rate formulas in obese children seems to provide no additional information.

Abstract

Background: There is growing interest in the relationship between obesity and renal damage. The effect of obesity on renal function in children and adolescents has not been adequately investigated. In addition, there is no complete consensus on the reliability of renal function parameters and which of these accurately estimate true renal function. The primary goal of this study was to evaluate renal function in obese children and adolescents using glomerular filtration rate (GFR), cystatin C, and creatinine (Cr)-derived formulas. We also compared classical GFR measurement methods with methods based on bioimpedance analysis-derived body cell mass (BCM).

Subjects and Methods: We enrolled 108 obese and 46 healthy subjects aged 6–18 years. Serum cystatin C, serum creatinine, 24-hour proteinuria, creatinine clearance (CrCl), and GFR were evaluated in both groups. Estimated GFR was measured with creatinine-based, cystatin C-based, combined (cystatin C and creatinine), and BCM-based formulas. Both actual and fat-free mass body surface areas were used when required. Metabolic parameters (blood glucose, insulin, and lipids) were analyzed in the obese subjects, and International Diabetes Federation criteria were used to identify metabolic syndrome (MetS).

Results: We did not detect statistically significant differences between the obese and control groups for mean creatinine (p=0.658) and mean cystatin C (p=0.126). Mean cystatin C levels of MetS patients were significantly higher than in non-MetS obese participants. Creatinine-based GFR measurements, BCM-based measurements, and a combined creatinine and cystatin C measurement showed a statistically significant increase in the GFR of obese subjects compared to controls. This increase was negatively correlated with duration of obesity. Estimations also did not differ based on actual or fat-free mass body surface area. Only the Filler equation showed a statistically significant decrease in eGFR in MetS patients. There were no statistically significant

differences between the obese and control groups for proteinuria (p=0.994) and fat-free mass proteinuria (p=0.476).
Conclusion: We conclude that cystatin C could be used as an earlier biomarker than creatinine in the detection of impaired renal function in obese children, especially those with MetS. Creatinine-based formulas represent hyperfiltration as the first difference in renal function. Decreasing eGFR seen with cystatin C-based formulas in MetS patients but not creatinine-based formulas may represent the early stages of renal damage. Using fat-free mass or BCM for eGFR formulas in obese children seems to provide no additional information.
Key words: Obesity, glomerular filtration rate, body cell mass, cystatin C

INTRODUCTION

Obesity is a serious health problem that adversely affects whole-body systems, particularly the cardiovascular and endocrine systems (1). Among the adverse effects of obesity, kidney problems have recently begun to attract more attention. Increased obesity-related glomerulopathy has become apparent in the last 20 years as the role of obesity in the onset and progression of adult kidney disease has been better defined (2). With increased obesity prevalence, a significant increased prevalence of chronic kidney disease (CKD) and end-stage renal failure has been observed in the last 30 years (2). Vivente et al. found that overweight and obesity were serious risk factors for end-stage renal failure in their 30-year survey of 1.2 million adolescents (3). Obesity was also found to be associated with negative effects on allograft and reduced allograft survival in patients undergoing renal transplantation (4).

The effects of obesity and metabolic syndrome (MetS) on renal function have not been sufficiently investigated in children and adolescents. In addition, there is no consensus on the reliability of renal function parameters and which of these represent true renal function (4). The glomerular filtration rate (GFR) is one of the most important parameters used to determine renal function, and can be calculated with different formulas. GFR is generally calculated with body surface area (BSA)-based formulas; however, these calculations may give incorrect results, particularly for obese children due to a higher BSA than in normal-weight children. Cystatin C is a biomarker recommended for use in GFR calculations because it is easily glomerular-filtered, has a low molecular weight, and is not dependent on muscular mass (5,6). Studies have indicated that cystatin C-derived formulas provide more accurate results than conventional GFR calculation methods (6). However, both conventional GFR formulas and cystatin C-derived formulas may be affected by the amount of adipose tissue, so calculation of GFR based on non-adipose tissue is considered a more accurate method (7). Proteinuria, one of the best predictors of renal damage, is another parameter that should be considered in renal function evaluations (8).

The primary goal of the present study was to extensively evaluate the renal function of obese children and adolescents using serum cystatin C levels, cystatin C- and creatinine-based eGFR, and proteinuria. We also investigated the relationship between these parameters and MetS components and obesity duration. Furthermore, we compared classical GFR measurement methods with those based on bioimpedance analysis-derived body cell mass (BCM) and fat-free mass BSA.

MATERIAL AND METHODS

Study Design

This prospective observational study was conducted between January 2014 and January 2015 at the pediatric endocrinology outpatient clinic of Ankara University School of Medicine. All participants or parents gave informed consent for participation. Institutional ethics committee approval was also obtained. On 23 September 2013, the decision of the Ankara University Ethics Committee, No. 14-540-15, was taken for our study titled 'Control of renal function in obese children and adolescents and relation with metabolic syndrome components'. Project support was obtained from the Association of Pediatric Endocrinology and Diabetes.

Patient Enrollment

We enrolled consecutive patients aged 6–18 years with a body mass index (BMI) in the >95th percentile. We excluded patients with comorbidities (diabetes mellitus, congenital heart disease, and chronic systemic disorders) and those who were receiving systemic drugs at the time of admission. Normal-weight (BMI <85th percentile) healthy subjects formed the control group.

Measures and Outcomes

The demographic data (age, gender, and duration of obesity) and physiologic measurements (weight, height, height standard deviation score [SDS], BMI, blood pressure, and pubertal stage) of the participants were recorded. Laboratory evaluations were performed, including fasting plasma glucose, fasting plasma insulin, blood creatinine, cystatin C, blood total cholesterol, blood low-density lipoprotein cholesterol (LDL-C), blood high-density lipoprotein cholesterol (HDL-C), blood triglycerides, and 24-hour urine protein and urine creatinine levels. Cystatin-C was measured by Nephelometric immunoassay. The homeostatic model assessment-insulin resistance (HOMA-IR) of each patient was calculated. HOMA-IR levels of >2.22 in prepubertal girls, >2.67 in prepubertal boys, >3.82 in pubertal girls, and >5.22 in pubertal boys were accepted as demonstrating insulin resistance (9). The body-fat mass of each participant was measured with a bioimpedance analyzer (Tanita®) to

compare GFR, cystatin C levels with BCM and creatinine clearance (CrCl) Both BSA (for CrCl) and fat-free mass BSA (adopted using total fat-free mass in GFR formulas as body weight) were analyzed. BCM was calculated as intracellular fluid divided by 0.70 (7). We identified MetS patients, 10–18 years old, based on the International Diabetes Federation (IDF) MetS criteria (10). The IDF criteria define MetS as central obesity (waist circumference >90th percentile) combined with any two of the following: dyslipidemia (triglycerides >150 mg/dl), reduced HDL-C (<40 mg/dl), increased blood pressure (systolic >130 mmHg or diastolic >85 mmHg), increased fasting plasma glucose (>100 mg/dl), or previously diagnosed type 2 diabetes.

For the GFR measurements, we used four groups of formulas: creatinine-based, cystatin C-based, combined (creatinine- and cystatin C-based), and BCM-based (Table 1) (11-18). We used only creatinine-based formulas for GFR measurements with fat-free cell mass.

For evaluation of proteinuria, 24-hour urine samples were collected. Protein excretion of 100 mg/m^2/day indicated nephritic, while >1 gr/m^2/day indicated a nephrotic level (19). Fat-free mass adjusted proteinuria was also calculated.

Statistical Analysis

Statistical analysis was performed using SPSS software (SPSS 20.0 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD or median (minimum-maximum), and nominal variables were expressed as numbers (%) in the descriptive analyses. Percentage comparisons of groups were performed using the Chi-square test, and multivariate logistic regression analyses were performed for statistically significant variables. Normally distributed variables were compared using the t test, and non-normally distributed variables were compared using the Mann-Whitney U test. For all statistical analyses, $p<0.05$ was considered significant.

RESULTS

Clinical Characteristics of Participants

A total of 154 children and adolescents were enrolled in the study. Of these, 108 were in the obese group and 46 were in the control group. The age and gender distributions of the two groups were similar. The mean age was 13.2±2.7 (6.1–18) years in the obese group and 12.9±3.6 (7.5–17.6) years in the controls. Weight ($p<0.001$), height ($p<0.001$), BMI ($p<0.001$), BMI SDS ($p<0.001$), height SDS ($p<0.001$), and waist circumference ($p<0.001$) were greater in the obese group than in the control group (Table 2). Laboratory analysis of all cases were given at Table 3. Based on the IDF criteria, MetS was identified in 14.8% of the obese participants and none of the control participants.

Creatinine and Cystatin C Results

Serum creatinine and cystatin C levels were compared to evaluate renal function. There were no statistically significant differences between the obese and control groups' mean levels of creatinine ($p=0.658$) and cystatin C ($p=0.126$) (Table 4). The mean levels of cystatin C in the obese children with MetS were significantly higher than in the controls and the non-MetS obese participants.

We performed Spearman's correlation and a regression analysis to evaluate the factors affecting cystatin C and creatinine levels. There was a positive correlation between cystatin C and total cholesterol ($r=0.275$, $p=0.001$), LDL-C ($r=0.277$, $p<0.001$), triglycerides ($r=0.318$, $p<0.001$), and fasting insulin (r-0.255, $p=0.001$). There was an inverse correlation with HDL-C ($r=-0.219$, $p=0.006$). There was no significant correlation between creatinine and total cholesterol ($r=-0.085$, $p=0.296$), LDL-C ($r=-0.098$, $p=0.225$), HDL-C ($r=0.091$, $p=0.260$), triglycerides ($r=0.11$, $p=0.889$), fasting plasma glucose ($r=0.016$, $p=0.840$), and fasting insulin ($r=0.133$, $p=0.101$).

Renal Function Evaluation Based on GFR Formulas

The obese patients' GFR results that were calculated with the CrCl, fat-free mass CrCl, Bedside Schwartz (13), Andersen et al. (7), Donadio et al. (2004) (18), and Donadio et al. (1998) (17) formulas were statistically significantly higher than in the control group. In the obese group without MetS, the GFR results calculated with the CrCl and Bedside Schwartz formulas were higher than in the control group ($p<0.05$). The GFR values calculated with the cystatin C-derived Filler formula and the cystatin C and serum creatinine-derived Bouvet formula were lower in the MetS-diagnosed obese patients than in the non-MetS obese patients and the controls ($p<0.05$). In both the MetS obese group and the non-MetS obese group, GFR levels calculated with fat-free mass CrCl, Andersen et al.'s formula, Donadio et al.'s formula (2004) (18), and Donadio et al.'s formula (1998) (18) were higher than in the control group (Table 5). As the duration of obesity is increased, GFR calculated with Donadio et al.'s both formula (17,18) increased, but GFRs calculated with Filler ($p=0.08$) , Bouvet ($p=0.020$), and Bedside Schwartz ($p=0.038$) were decreased.

Renal Function Evaluation Based on Proteinuria

There were no statistically significant differences between the obese and control groups for proteinuria ($p=0.994$) and fat-free mass proteinuria ($p=0.476$) (Table 6). There were also no statistically significant differences between the MetS obese, non-MetS obese, and control groups with regard to proteinuria and fat-free mass

proteinuria results. Nephritic-range proteinuria was detected in 12 non-MetS obese participants (11.1%) and in 6 control-group participants (12%). Nephrotic-range proteinuria was not detected in any of the participants.

DISCUSSION:

Obesity has a harmful effect on renal function, so determining exact renal function is more important in obese patients than in those of normal weight. One of the most useful parameters of renal function is eGFR. Accurate calculation of GFR has a vital role in the accurate identification of kidney disease, drug-dose calculations, CKD management, and prognostic predictions (20). There are several models for GFR measurements, but none are accepted as ideal methods alone (7). There is a potential risk that creatinine-based formulas may give GFR results that are lower in obese patients than even in normal-weight individuals. Since CrCl is affected by situations such as acute and chronic disease, it is reported that this method is not very sensitive for GFR (21). However, among the GFR measurement methods, CrCl is used by clinical laboratories at a rate as high as 80% (20). It is accepted that serum cystatin C gives more accurate GFR calculations because it is less affected than creatinine by muscle mass and diet (22). Roos et al. compared 24 cystatin C and creatinine studies involving a total of 2,007 participants(23). They found that at a 95% confidence interval and according to the Moses-Littenberg linear regression model, cystatin C was more interoceptive for indicating renal dysfunction compared to creatinine (cystatin C: 3.99 [3.41–4.57] versus creatinine: 2.79 [2.12–3.4]) (23).

"There are an increasing number of studies about eGFR, Cistation-C measurements during childhood. One of these studies has been done by Miliku K, et al.. They compared the relationship between body composition and eGFR which is calculated based on creatinin and cystatin-C concentrations. They found that, eFGR was influenced by BMI and BSA. Moreover, eFGR that has been based on creatinin concentrations, was also influenced by lean mass percentage and fat mass percentage of the patients(24). This study was limited to 6 year-old healthy children. In another study, Correia-Costa L, et al. evaluated 163 normal and 150 overweight/obese children, ranging from 8 to 9 years of age. They compared eGFR, CrCl, creatinin and cystatin-C levels of the patients. Results showed that, overweight/obese children had lower eGFR values using several formulas except the ones with CrCl and Schwartz formula (25).

In the present study, kidney function of obese participants was thoroughly assessed with creatinine-based, cystatin C-based, combined creatinine and cystatin C, and BCM-based GFR formulas and with proteinuria levels. We calculated the BCM and fat-free mass of obese participants from BSA-based GFR measurement techniques based on the hypothesis that the increased BSA of these participants may lead to inaccurate results. In a new model, Andersen et al. found that both the BCM and the weight models are reliable methods for estimating GFR in children, with a higher accuracy than the currently recommended Schwartz model (7). To the best of our knowledge, our study is the first to use the Andersen method. We did not find any differences between using the BCM model and CrCl methods. However, we obtained similar results using fat-free cell mass for GFR calculations with creatinine-based formulas. We obtained higher GFR values in the obese group compared to the control group using calculations with combined creatinine and cystatin C (Donadio et al. 1998) and all BCM or creatinine-based formulas. We consider that the increased GFR with creatinine-based formulas in this study support the hyperfiltration and renal-function effects in obese participants. However, there was no difference between GFR rates using the cystatin C-based formulas of Filler et al. and Zappitelli et al. We believe that this is due to parallel cystatin C levels between the obese and control groups.

We detected higher cystatin C levels in the MetS-diagnosed obese group compared to the non-MetS obese group as an indicator of renal damage. Cystatin C is recommended as an interoceptive biomarker indicating kidney function when creatinine levels are not yet affected, such as during the early stages of kidney damage and with mildly decreased GFR (7). Cystatin C is less affected by muscle mass and diet compared to creatinine; therefore, it should be used instead of creatinine for more accurate GFR measurements (22). Research by Marwyne et al. showed that cystatin C gave more accurate results compared to creatinine in abnormal GFR measurements when compared to ^{99}mTc-DTPA ($r=0.526$, $p=0.001$)(26). Some pediatric researchers have made comparisons between cystatin C and creatinine in terms of predicting renal damage. In five of 12 studies done using ROC analyses, it was confirmed that cystatin C was significantly more sensitive than creatinine, but another five studies did not find any statistically significant difference between the biomarkers. In the remaining two studies, statistical comparisons were not performed. In one study, cystatin C was significantly predominant, while creatinine was not predominant to cystatin C in any of these 12 studies (7). Our present results showed that elevated serum cystatin C is an earlier biomarker than elevated serum creatinine in the detection of impaired renal function in obese children. Furthermore, in cystatin C-based formulas, a steady decline in GFR parallel to the duration of obesity may be assessed as an indicator that functional damage converted to structural damage over time. Based on these results, we conclude that creatinine-based formulas may not reflect real renal function due to giving inaccurate higher GFRs, particularly during the early stages of renal damage in obese participants.

With regard to GFR estimations using creatinine- or cystatin C-based formulas, the question was raised whether decreased GFR in obese children can be overlooked with increased cystatin C levels when using these formulas. We believe that since cystatin C increases with renal function impairment, it can be useful when GFR begins to decrease.

Dyslipidemia is a metabolic parameter that shows increased risk of renal failure. As a result of reabsorption of fatty acids and cholesterol from tubular epithelial cells, tubulointerstitial inflammation may stimulate foam cell formation and tissue damage. At the same time, dyslipidemia may damage mesangial cells and glomerular capillary endothelial cells, such as podocytes. Hypercholesterolemia and hypertriglyceridemia are relevant to podocyte damage. Accumulation of lipoproteins in the glomerular mesangium may stimulate matrix production and glomerulosclerosis (8). This hypothesis led to the idea of investigating the effect of dyslipidemia in CKD etiology. In a study done by Servais et al. on 925 dyslipidemic patients, cystatin C values were significantly high in patients with MetS and were correlated with dyslipidemia (27). In our study, in accordance with the literature, cystatin C values were found to significantly high in patients with MetS; the Spearman analysis showed positive correlations between cystatin C and total cholesterol, triglycerides, and LDL-C, but a negative correlation with HDL-C. This outcome shows that cystatin C is more accurate than creatinine as a biomarker for detecting the negative effects of dyslipidemia on renal function in obese children.

When we assessed our results in terms of proteinuria, we found no statistically significant difference between the obese and control groups. In addition, we found no statistically significant difference between the control and obese groups with and without MetS. Proteinuria and microalbuminuria are accepted as indicators, as well as risk factors, for chronic renal failure(28). BMI is the second most common factor after proteinuria in increased risk of end-stage renal failure. Obesity-related renal disease involves a wide spectrum of disorders, from excretion of urinary albumin to proteinuria and/or decreased GFR. The adverse effects of fat accumulation on kidney hemodynamics and obesity-related glomerulopathy are two important possible mechanisms for this. Hemodynamic changes cause inflammation, oxidative stress, apoptosis, and finally the development of renal scarring (29). The absence of significant differences between our study groups in terms of proteinuria indicates that no apparent structural renal damage had begun in our participants during the study period. Studies examining the relationship between renal protein loss and MetS have reported that increased albuminuria and proteinuria or the presence of microalbuminuria are risk factors for MetS (8). However, the common conclusion in the current literature is that protein loss does not increase the risk of MetS, unlike chronic renal failure development(30). We believe that proteinuria is not useful for indicating damaged renal function in obese pediatric patients.

Study limitations: Measurement of Inulin clearence as a valuable tool for GFR estimation could not be possible for our study groups.

Conclusion

Serum cystatin C can be used as an earlier biomarker than creatinine-based GFR estimations in the detection of impaired renal function in obese children, especially those with MetS. In a comparison of GFR measurement formulas, we found that creatinine-based formulas may give normal or higher GFR results, particularly during the early stages of renal dysfunction in obese children. Proteinuria is not an appropriate early biomarker for indicating damaged renal function. However, cystatin C could be a more sensitive biomarker compared to creatinine-based GFR estimations for the detection of dyslipidemia's negative effects on renal function in obese children. It appears that there is no need to use fat-free mass or BCM for determining eGFR in obese children.

1. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser [Internet]. 2000;894:i–xii, 1-253. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11234459
2. Gunta SS MR. Is obesity a risk factor for chronic kidney disease in children? Pediatr Nephrol 2013; 28. 2013;(28):1949–56.
3. Vivante A, Golan E, Tzur D, Leiba A, Tirosh A, Skorecki K, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Arch Intern Med [Internet]. 2012;172(21):1644–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23108588
4. Espinoza R, Gracida C, Cancino J, Ibarra A. Effect of Obese Living Donors on the Outcome and Metabolic Features in Recipients of Kidney Transplantation. Transplant Proc. 2006;38(3):888–9.
5. Samyn M, Cheeseman P, Bevis L, Taylor R, Samaroo B, Buxton-Thomas M, et al. Cystatin C, an easy and reliable marker for assessment of renal dysfunction in children with liver disease and after liver transplantation. Liver Transpl [Internet]. 2005;11(3):344–9. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15719405
6. Simonsen O, Grubb A TH. The blood serum concentration of cystatin C (gamma-trace) as a measure of

the glomerular filtration rate. Scand J Clin Lab Investig. 1985;45(2):97–101.
7. Andersen TB. Estimating renal function in children: a new GFR-model based on serum cystatin C and body cell mass. Danish medical journal. 2012.
8. Wickman C, Kramer H. Obesity and Kidney Disease: Potential Mechanisms. Semin Nephrol. 2013;33(1):14–22.
9. Kurtoğlu S, Hatipoğlu N, Mazıcıoğlu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. J Clin Res Pediatr Endocrinol [Internet]. 2010;2(3):100–6. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3005684&tool=pmcentrez&rendertype=abstract
10. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome [Internet]. The IDF consensus worldwide definition of the metabolic syndrome. 2006. p. 1–7. Available from: http://www.idf.org/webdata/docs/MetS_def_update2006.pdf
11. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med. 2006;354:2473–83.
12. Du Bois D, Du Bois EF. Clinical calorimetry: tenth paper a formula to estimate the approximate surface area if height and weight be known. Arch Intern Med. 1916;17(6_2):863–71.
13. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009; 20(3):629-37.
14. Filler G, Lepage N. Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? Pediatr Nephrol. 2003;18(10):981–5.
15. Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, et al. Derivation and validation of cystatin C-based prediction equations for GFR in children. Am J Kidney Dis [Internet]. 2006;48(2):221–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16860187
16. Bouvet Y, Bouissou F, Coulais Y, Séronie-Vivien S, Tafani M, Decramer S, et al. GFR is better estimated by considering both serum cystatin C and creatinine levels. Pediatr Nephrol [Internet]. 2006;21(9):1299–306. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16794818
17. Donadio C, Lucchesi A, Tramonti G, Bianchi C. Creatinine clearance can be predicted from plasma creatinine and body composition analysis by means of electrical bioimpedance. Renal Failure. 1998.
18. Donadio C, Consani C, Ardini M, Caprio F, Grassi G, Lucchesi A. Prediction of glomerular filtration rate from body cell mass and plasma creatinine. Curr Drug Discov Technol [Internet]. 2004;1(3):221–8. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=16472249 http://oxfordsfx.hosted.exlibrisgroup.com/oxford?sid=OVID:medline&id=pmid:16472249&id=doi:&issn=1570-1638&isbn=&volume=1&issue=3&spage=221&pages=221-8&date=2004&title=Cu
19. Utsch B, Klaus G. Urinalysis in children and adolescents. Dtsch Arztebl Int [Internet]. 2014;111(37):617–25; quiz 626. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4187024&tool=pmcentrez&rendertype=abstract
20. Inker L a, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med [Internet]. 2012;367(1):20–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22762315
21. Levey AS, Stevens L a, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
22. Tangri N, Stevens L a, Schmid CH, Zhang YL, Beck GJ, Greene T, et al. Changes in dietary protein intake has no effect on serum cystatin C levels independent of the glomerular filtration rate. Kidney Int [Internet]. 2011;79(4):471–7. Available from: http://dx.doi.org/10.1038/ki.2010.431
23. Roos JF, Doust J, Tett SE, Kirkpatrick CMJ. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children-A meta-analysis. Clin Biochem. 2007;40(5–6):383–91.
24. Miliku K, Bakker H, Dorresteijn EM, Cransberg K, Franco OH, Felix JF, Jaddoe VW. Childhood Estimates of Glomerular Filtration Rate Based on Creatinine and Cystatin C: Importance of Body Composition. Am J Nephrol. 2017;45(4):320-326.
25. Correia-Costa L, Afonso AC, Schaefer F, Guimarães JT, Bustorff M, Guerra A, Barros H, Azevedo A. Decreased renal function in overweight and obese prepubertal children. Pediatr Res. 2015 Oct;78(4):436-44.
26. M N Norli Marwyne, MMED, C Y Loo, MMED, A G Halim, MMED, K Norella, FRACP, T Sulaiman MsN, Medicine, M I Zaleha P. Estimation of Glomerular Filtration Rate using Serum Cystatin C in Overweight and Obese Subjects. Med J Malaysia. 2011;66(4):313–7.
27. Servais A, Giral P, Bernard M, Bruckert E, Deray G, Isnard Bagnis C. Is serum cystatin-C a reliable marker for metabolic syndrome? Am J Med [Internet]. 2008;121(5):426–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18456039
28. Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD. Metabolic syndrome

and kidney disease: a systematic review and meta-analysis. Clin J Am Soc Nephrol [Internet]. 2011;6(10):2364–73. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3186450&tool=pmcentrez&rendertype=abstract
29. Redon J, Lurbe E. The kidney in obesity. Curr Hypertens Rep [Internet]. 2015;17(6):555. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84928402298&partnerID=tZOtx3y1
30. Prasad GVR. Metabolic syndrome and chronic kidney disease: Current status and future directions. World J Nephrol [Internet]. 2014;3(4):210–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4220353&tool=pmcentrez&rendertype=abstract

Table 1. Formulas used for GFR calculations (11-18)

Creatinine-based formulas
Creatinine clearance = (urine creatinine [mg/dL] × urine volume [mL] × 1.73) / (serum creatinine [mg/dL] × 1440 × m² [BSA]) (ml/minute/1.73 m²) (11) BSA = 0.007184 × height (cm) $^{0.715}$ × weight (kg)$^{0.425}$) (12)
Fat-free mass creatinine clearance: (urine creatinine [mg/dL] × urine volume [mL] × 1.73) / (serum creatinine [mg/dL] × 1440 × m² [fat-free mass BSA]) (ml/minute/1.73 m²) (11) Body surface area: 0.007184 × height (cm) $^{0.715}$ × fat-free mass (kg) $^{0.425}$(12)
Bedside Schwartz: 0.413 × height (cm) / serum creatinine (mg/dL) (13)
Cystatin C-based formulas
Filler formula: 91.62 × (1/cystatin C)$^{1\text{-}123}$ (14) Cystatin C = mg/L
Zapitelli formula: 75.94 / cystatin C $^{1.17}$ (renal transplant patients × 1.2) (15) Cystatin C= mg/L
Creatinine- and cystatin c-based formulas
Bouvet's formula: 38.4 × (serum creatinine)$^{-0.35}$ × (cystatin C)$^{-0.56}$ × (weight [kg])$^{0.30}$ × (age)$^{0.40}$ ml/minute) (16) Serum creatinine: mg/dL; cystatin C: mg/L
Donadio et al.'s (1998) formula: 0.426 × (weight [kg]) / cystatin C)$^{0.39}$ × (height [cm] × BSA / serum creatinine)$^{0.64}$ (17) Serum creatinine: mg/dL; cystatin C: mg/L
Body cell mass formulas
Andersen et al.'s formula: 10.2 × (BCM / cystatin C)$^{0.40}$ × (height × BSA/serum creatinine) $^{0.65}$ GFR: ml/minute; serum creatinine: mmol/L; serum creatinine: mg/dL × 88.4 BCM (kg) = intracellular fluid / 0.7 (7)
Donadio et al.'s (2004) formula: (BCM × 2,231 / serum creatinine) – 2,73 BCM (kg) = intracellular fluid / 0.7 (18)

Table 2: Clinical characteristics of all cases

	Obese group (n:108) Mean ±SD	**Control group (n:46) Mean ±SD**	**P values**
Male: Female :	47 (%43,5) 61 (%56,5)	21 (%45,7) 25 (%54,3)	0,860
Pubertal/prepubertal (N)	88/20	25/21	**0,002**
Age (years)	**13,2 ±2,7** (6,1-18)	**12,9 ±3,6** (7,5-17,6)	0,209
Height (cm)	**156,6±12,6** (116,7-187,3)	**144,3±17,1** (117,5-176)	**<0,001**
Heigh SDS	**0,48±0,98** (-1,76-3,18)	**-0,38±0,92** (-2,25-1,53)	**<0,001**
Body weight (kg)	**71,1±19,3** (26,5-124,6)	**38,7±14,4** (19-63)	**<0,001**
BMI (kg/m²)	**28,3±4,5** (19,4-42,3)	**17,8±3,3** (12,4-24,8)	**<0,001**
RVKİ	**142,9±18,3** (115,5-217,8)	**92,8±11,4** (68,6-119)	**<0,001**
VKİ SDS	**2,2±0,63** (1,1-3,8)	**-0,57±1,11** (-3,48-1,18)	**<0,001**
Waist circumference (cm)	**87,7±10,7** (65-120)	**58,9±8** (48-82)	**<0,001**

Table 3: Laboratory characteristics of all cases

	Obese cases (n:108) mean ± SD	**Control (n:46) Ort ± SS**	**P values**
Fasting blood glucose (mg/dL)	**84,8±8,0** (57,0-102,0)	**78,3±8,1** (50,0-94,0)	**<0,001**
Fasting insulin (mIU/mL)	**17,4±7,1** (3,0-41,9)	**7,7±3,6** (1,5-17,1)	**<0,001**
Total Cholesterol (mg/dL)	**167,3±36,7** (85,0-277)	**154,2±25,6** (117-211)	0,032
LDL- Cholesterol (mg/dL)	**102,1±30,9** (45,0-208,0)	**87,8±24,5** (45,0-145,0)	**0,007**
HDL-Cholesterol (mg/dL)	**44,7±10,3** (26,0-76,0)	**49,2±10,1** (30,0-75,0)	**0,007**
VLDL-Cholesterol (mg/dL)	**21±11,4** (5,0-52,0)	**17,1±7,2** (3,0-35,0)	**0,140**
Triglyceride (mg/dL)	**104±56,6** (26,0-262,0)	**85,3±36,2** (17,0-177,0)	**0,156**

Table 4. Serum creatinine and cystatin C levels

	All obese patients (n=108) Mean±SD	Non-MetS obese patients (n=92) Mean±SD	MetS obese patients (n=16) Mean±SD	Control (n=46) Mean±SD	P value
Creatinine (mg/dL)	0.5±0.11 (0.28–0.88)	0.5±0.11 (0.28–0.88)	0.54±0.15 (0.35–0.79)	0.52±0.15 (0.23–0.91)	0.649
Cystatin C (mg/L)	0.69±0.12 (0.35–1.08)	0.67±0.11 (0.35–0.93)	0.8±0.12 (0.66–1.08)	0.66±0.1 (0.5–0.93)	<0.001

Table 5. Comparison of GFR measurement methods in obese subjects with and without MetS and the control group

	GFR measurement method	Control (n=46)	All obese patients (n=108)	Obese without MetS (n=92) Mean±SD	Obese with MetS (n=16) Mean±SD	P 1	P 2
Creatinine-based formulas	**Creatinine clearance (ml/min/1.73 m²)** (11)	125.3±38.1 (74–212)	171.4±82.5 (51–473)	173.2±83.4* (65–473)	161.3±78.9* (51–330)	**<0.001**	**0.001**
	Fat-free mass creatinine clearance (ml/min/1.73 m²) (11)	147±45.8 (88–250)	215.5±102.3 (65–578)	218.2±104* (81–578)	200±93.4* (65–410)	**<0.001**	**<0.001**
	Bedside Schwartz (13)	118.2±26.9 (77–194)	131.5±25.9 (76–225)	132±25.1 (76–225)	129.1±31.2 (87-180.5)	**0.004**	**0.012**
Cystatin C-based formulas	**Filler** (14)	143.7±20.4 (101.5–186)	139±26.1 (87.9–264.8)	141.5±29.2 (101.5–264.8)	118.5±15.9 (87.9–141.9)	0.116	**<0.001**
	Zapitelli (15)	121.2±21.5 (82.6–166.9)	123.2±27.5 (69.4–259.3)	123.9±29 (69.4–259.3)	119.2±16.8 (94.4–1149.6)	0.862	0.894
Creatinine and cystatin C combined	**Bouvet** (16)	124±17 (88.1–159)	121.7±21.6 (79–224.8)	124.4±21.3 (90.7–224.8)	106±16 (79–141.3)	0.223	**0.002**
	Donadio et al. (1998) (17)	89±29.1 (46.5–161)	147±34.8 (70.3–256.8)	148.3±36.4 (70.3–256.8)	145.6±24.4 (82.1–172.7)	**<0.001**	**<0.001**
BCM-based formulas	**Andersen et al.** (7)	119±35.7 (61–191)	183.3±43.1 (78.2–323.8)	183.6±44.9 (78.2–323.8)	181.5±31.2 (103.4–212)	**<0.001**	**<0.001**
	Donadio et al. (2004) (18)	156±51.6 (79.1–278)	242.1±77.8 (88.5–557.1)	237.7±77.5 (88.5–557.1)	267.2±77.6 (120.4–391)	**<0.001**	**<0.001**

- Findings: mean ± standard deviation (min–max). P1 is indicated statistically significant correlations between obese group and control group, P2 is indicated statistically significant correlations between obese with metS and obese without MetS.
- BCM and GFR estimations calculated using fat-free mass BSA were similar to actual BSA-based GFR estimations.

Table 6. Proteinuria in obese cases with or without MS

	All obese cases Number (%)	Obese cases with MS Number (%)	Obese cases without MS Number (%)	Control group cases Number (%)
Proteinuria at nephritic level (4-40mg/m²/h)	**12 (%11)**	**0 (%0)**	**12 (%13)**	**6 (%12)**
Proteinuria at nephrotic level (>40mg/m²/h)	**0 (%0)**	**0 (%0)**	**0 (%0)**	**0 (%0)**
p value : 0,886				