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Assessment of renal functions with different glomerular filtration rate formulas in children with acute exposure of mercury

Akut civa maruziyeti olan çocuklarda renal fonksiyonların farklı glomerüler fitrasyon hızı formülleriyle değerlendirilmesi

Abstract: Objective: Our aim was to determine whether cystatin C level has a superiority to creatinine to assess kidney functions in rapid decreases of glomerular filtration rate due to acute mercury exposure in children. Eight different glomerular filtration rate calculation formulas which have been used creatinine and/or cystatin C were also compared.

Methods: Serum urea, creatinine and cystatin C values of 39 mercury exposed children were measured. Glomerular filtration rates were calculated by eight different formulas. Patient group was divided into three subgroups according to mercury levels.

Results: Cystatin C and mercury levels of the patients were found significantly different from control group (p<0.001). There was not a significant difference in creatinine and urea values between two groups (p=0.913, p=0.236). There was not a significant difference between patient and control groups in GFR calculations which have been used serum creatinine and height or which have been used urea additional to them (p=0.069, p=0.559, p=0.424, p=0.945, respectively), but there was a significant differ-ence between patient and control groups in GFR calculations which have been used cystatin C only or creatinine, urea and height in addition to this (p<0.001, p<0.001, p=0.042, p<0.001, respectively). In sugroup analysis, cystatin C results and the results of three GFR calculations of four GFR calculations which were used cystatin C were found different in control group according to subgroups but there was not a difference between subgroups.

Conclusion: Cystatin C level is a better indicator than creatinine to assess kidney functions in rapid decreases of glomerular filtration rate due to acute exposure of mercury. Formulas using cystatin C gave better results than formulas using creatinine and height in estimation of glomerular filtration rate.

Keywords: Mercury, cystatin C, creatinine, acute renal damage, glomerular filtration rate

Özet: Amaç: Çocuklarda akut civa maruziyetine bağlı hızlı glomerüler fitrasyon hızı azalmalarında sistatin C düze-yinin böbrek fonksiyonlarını değerlendirme açısından

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kreatinine üstün olup olmadığını belirlemeyi amaçladık. Ayrıca kreatinin ve/veya sistatin C kullanılan 8 ayrı glomerular filtrasyon hızı hesaplama formülünü birbiriyle karşılaştırdık.

Metod: Civa maruziyeti yaşayan 39 çocuğun serum üre, kreatinin ve sistatin C düzeyleri ölçüldü. Glomerular filtrasyon hızı 8 farklı formülle hesaplandı. Hasta grubu civa seviyelerine göre üç subgruba bölündü.

Bulgular: Hastaların sistatin C ve civa düzeyleri kontrol grubundan anlamlı olarak farklı bulundu (p<0.001). Kreatinin ve üre açısından iki grup arasında anlamlı bir fark bulunmadı (p=0.913, p=0.236). Serum kreatinini ve boy kullanılarak veya bunlara ilaveten üre değerleri kullanılarak yapılan GFR hesaplamalarında hasta ve kontrol grupları arasında anlamlı bir fark yokken (sırasıyla, p=0.069, p=0.559, p=0.424, p=0.945), yalnızca sistatin C veya buna ek olarak kreatinin, üre ve boyun kullanıldığı GFR hesaplamalarında hasta ve kontrol grupları arasında anlamlı bir fark vardı (sırasıyla, p<0.001, p<0.001, p=0.042, p<0.001). Subgrup analizinde sistatin C sonuçları ile sistatin C kullanılarak hesaplanan dört GFR hesaplamasından üç tanesine ait sonuçlar kontrol grubunda subgruplara göre farklı bulunurken subgruplar arasında farklı bulunmadı.

Sonuç: Akut maruziyetlere bağlı hızlı glomerüler fitrasyon hızı azalmalarında sistatin C düzeyi böbrek fonksiyonlarını değerlendirme açısından kreatinine üstündür. Sistatin C kullanılarak oluşturulan formüller glomerüler filtrasyon hızını belirlemede kreatinin ve boy uzunluğu kullanılarak oluşturulan formüllere kıyasla daha iyi sonuç vermektedir.

Anahtar Kelimeler: Civa, sistatin C, kreatinin, akut böbrek hasarı, glomerüler fitrasyon hızı

Introduction

Mercury, which exists as organic and inorganic forms, is a well-known heavy metal because of its toxic properties [1]. Besides occupational exposure, many other types of exposure have been reported in the literature [2–5]. Spills or crashing of mercury-containing materials have been seen many times, especially in school environment because of its attractive properties [6].

Although metallic mercury has been demonstrated to affect renal system primarily, there are many scientific reports or studies about its effects on many physiological systems, especially central nerve system [7–9].

The accurate calculation of glomerular filtration rate (GFR) is essential in the evaluation of renal functions. The usage of exogenous substances is not accepted to be practical in the calculation of "true" GFR, especially in ages of childhood. Although creatinine is the most frequent preferred biomarker in the calculation, many studies still try to find its alternative because of its weak properties that is easily affected from personal factors. Cystatin C is known to be a better biomarker presenting GFR because of its accuracy, even in changing individual factors [10–15].

While acute and high level exposure to toxic metals causes acute GFR changes, chronic and low level exposures can lead to mild clinical manifestations, which is really obscure that can prevent the accurate diagnosis. In these conditions, Cyctatin C seems to be a better biomarker than creatinine. The studies aiming the most accurate calculation of GFR are still continuing in scientific area [16–18].

There are generated formulas calculating GFR in children using serum creatinine and/or cystatin C concentrations. A few of these are formulas of Schwartz, Counahan, Filler, Zappitelli and collaborates [19]. As well as these formulas, KDIGO (Kidney Disease Improving Global Outcomes) 2012 Clinical Practice Guideline has suggested three pediatric GFR estimating equations [20]. (Table 1).

In this study we aimed to determine whether cystatin C level has a superiority to creatinine to assess kidney functions in rapid decreases of glomerular filtration rate due to acute mercury exposure in children. Eight different glomerular filtration rate calculation formulas which have been used creatinine and/or cystatin C were also compared.

Materials and Methods

Study population

In this retrospective study we eevaluated 39 children who were exposed to metallic mercury that has spilled on the floor via inhalation approximately 45 minutes. The patient group was composed of 15 girls and 24 boys. Mean age was 12.93±0.70 years for girls and 12.78±0.85 years for boys. In the patients' records, symptoms were reported as head-

Table 1: Formulas used in GFR calculations.

Reference	Formula	Type
Shwartz et al.	$[K \times height]/serum\ creatinine$	(GFRshw1)
Shwartz et al.	$39.1\ [height/serum\ creatinine]^{0.516} \times [1.8/cystatin\ C]^{0.294} \times [30/BUN]^{0.169} \times 1.099]^{male}[height/1.4]^{0.188}$	(GFRshw2)
Counahan et al.	$43.00\ [height/serum\ creatinine]$	(GFRcou)
Filler et al.	$91.62\ [1/cystatin\ C]^{1.123}$	(GFRfill)
Zappitelli et al.	$43.82\ [1/cystatin\ C]^{0.635}[1/serum\ creatinine]^{0.547}\ [1/35^{height}]$	(GFRzapp)
KDIGO2012	$41.3\ (height/SCr)$	(GFRkdigo1)
KDIGO2012	$40.7\ (height/SCr)^{0.64} \times (30/BUN)^{0.202}$	(GFRkdigo2)
KDIGO2012	$70.69\ (SCysC)^{-0.931}$	(GFRkdigo3)

GFR: mL/dk/1.73m²; K: 0.55 for girls, 0.70 for boys; height: meter, serum creatinine: mg/dL; blood urea nitrogen: mg/dL; cystatin C: mg/L.

ache, nausea, mid-dilated pupils and peripheral neuropathy. Patients were treated with 2,3-dimercaptopropanesulfonic acid (DMPS). The test results belong to 30 children, who referred to the hospital at the same period for routine examination were used as control data.

Patient group was divided into three subgroups according to mercury concentrations (Group 1: 10-20 ug/L, group 2: 20-30 ug/L, group 3: >30 ug/L).

The following data were extracted from the hospital database and patients' records: spot urine mercury, serum creatinine, cystatin C and urea levels, age, height and weight.

The study was approved by the Ethical Committee of Ankara Numune Education and Research Hospital and verbal informed consent was obtained from all patients.

Methods

Blood and urine samples were collected from patients who referred to the hospital in the morning. All samples were analyzed in the same day. Blood samples were drawn to 16x100 mm tubes with red caps not containing gel (BD Vacutainer). After at least 30 minutes incubation, the specimens were centrifuged at 1500xg for ten minutes. Serum creatinine levels were studied by enzymatic method and urea levels were studied by colorimetric method with Vitros 5.1 FS device (Ortho-Clinical Diagnostics, Rochester NY). Serum cystatin C levels were studied by particule surface expanded immunoturbidimetric method with Roche P 800 moduler device (Roche Diagnostics, Mannhein, Germany).

Serum creatinine method was traceable to a gas chromatography isotope dilution mass spectrometry (GC/IDMS) method and National Institute of Standards and Technology (NIST) SRM 914 creatinine standard reference material. Serum cystatin C method was standardized against an in-house reference preparation of pure recombinant human cystatin C. The cystatin C concentration of this reference preparation was established by dry mass determination as described in Bilrup-Jensen reference.

Mercury levels were determined in morning spot urine samples using Inductively Coupled Plasma Mass Spectrometry (ICP-MS) (Agilent 7700 series, Tokyo, Japan). Urine samples were collected in sterile plastic pots and then diluted 1 in 10 with 5% nitric acid solution. Standard solution of mercury was prepared by dilution of certified standard solutions (High Purity Standards, Charleston, SC, USA). Two levels quality control materials were used (Seronorm, Billingstad, Norway). Internal standard which was diluted 1/200 was containing bismuth, germanium, indium, lithium, lutetium, rhodium, scandium, and terbium. The mercury calibration curve ranged from 0 to 100 µg/L. Limit of detection and Limit of quantification were 0.02 and 0.1 µg/L respectively, Relative Standard Deviation % of measurements was 5.6.

Statistical Analysis

Statistical analysis of data was made by using SPSS (Version 15.0) (SPSS Inc, Chicago, IL, USA) package program. Coherence to normal distribution analysis was made by using Kolmogorov-Smirnov test. Values were presented as mean±SD or in the case of non-normally distributed data, as median (25th-75th percentiles). The presence of a statistically significant difference between the groups in terms of continuous variables was examined with Student's T test for parametric variables and Mann–Whitney U test for non-parametric variables. Subgroup analyses were done by one-way ANOVA followed by Tukey analysis for parametric variables. Nonparametric analysis was conducted using the Kruskal-Wallis test. Gender-specific differences on measured and calculated values were examined using the Chi-square test. All results were accepted statistically significant for $p<0.05$.

Table 2: Comparison of control group data and patient group data.

	Control group (n=30)	Patient group (n=39)	P value
Mercury (ug/L)	3.90 (0.02-6.08)	22.95 (10.50-57)	<0.001
Creatinine (mg/dL)	0.60 (0.40-0.70)	0.50 (0.40-0.70)	0.913
Urea (mg/dL)	23.54 (19.26-38.52)	25.68 (17.12-47.08)	0.236
Cystatin C (mg/L)	0.89±0.13	1.09±0.12	<0.001
GFRshw1 (mL/dk/1.73m²)	162.24 (126-214)	171.24 (124-221)	0.069
GFRcou (mL/dk/1.73m²)	118.25 (98-165)	129.2 (96-165)	0.559
GFRfill (mL/dk/1.73m²)	107.14±14.57	83.91±10.34	<0.001
GFRzapp (mL/dk/1.73m²)	106.61±12.27	94.03±11.66	<0.001
GFRshw2 (mL/dk/1.73m²)	103.78±11.83	99.33±9.02	0.042
GFRkdigo1(mL/dk/1.73m²)	113 (94-158)	123 (92-159)	0.424
GFRkdigo2(mL/dk/1.73m²)	96.49±11.97	96.31±10.41	0.945
GFRkdigo3(mL/dk/1.73m²)	79.43±9.6	65±6.7	<0.001
Age (years)	12.21±0.96	12.85±0.77	0.002
Height (cm)	152.93±6.60	157.33±6.02	0.005
Weight (kg)	43.8±8.60	42.6±7.50	0.560

The data are given as median (25th-75th percentiles) or Mean±SD.

Results

Median mercury concentrations of patient and control groups were 21.96 (11.25-116.9) and 2.61 (0.04-7.3) mg/g creatinine, respectively. Median urea concentration were 23.54 (19.26-38.52) mg/dL or 8.40 (6.87-13.75) mmol/L for control group, 25.68 (17.12-47.08) mg/dL or 9.16 (6.11-16.80) mmol/L for patient group. Median creatinine concentrations of control and patient groups were 53.04 (35.36-61.88) μmol/L and 44.2 (35.36-61.88) μmol/L, respectively. Mean and median values belonging to patient and control groups were given in Table 2.

The mean cystatin C values of control and patient groups were 0.89±0.13 mg/L and 1.09±0.12 mg/L (66.6±9.73 nmol/L and 81.6±8.98 nmol/L, respectively) respectively (p<0.001) (Figure 1). There was no significant difference between two groups in terms of creatinine and urea values (p=0.913, p=0.236).

In GFR calculations using GFRfill, GFRzapp, GFRshw2 and GFRkdigo3 equations, significant difference was determined between results of control and patient groups (p<0.001, p<0.001, p=0.042, p<0.001, respectively). In GFR calculations using GFRshw1, GFRcou, GFRkdigo1 and GFRkdigo2 equations important significant difference was not determined between results of control and patient groups (p=0.069, p=0.559, p=0.424, p=0.945, respectively).

In the subgroup analysis there was not a significant difference between control group and subgoups for creatinine, urea, GFRshw1, GFRcou, GFRshw2, GFRkdigo1 and GFRkdigo2 values (p=0.884, p=0.665, p=0.334

p=0.716 p=0.242, p=0.762, p=0.984, respectively). In all subgroups, cystatin C values were found to be higher than the control group, GFRfill, GFRzapp and GFRkdigo3 values were found to be lower than the control group (p<0.001, p<0.001, p=0.001, p<0.001, respectively), however, there was not a significant difference between the subgroups (Table 3).

According to Chi-square test it was determined that gender had no effect on parameters of mercury, creatinine, urea, cystatin C, GFRshw1, GFRcou, GFRfill, GFRzapp, GFRshw2, GFRkdigo1 GFRkdigo2 and GFRkdigo3 (p=0.471, p=0.726, p=0.808, p=0.482, p=0.238, p=0.674, p=0.528, p=0.470. p=0.443, p=0.250, p=656, p=454 respectively).
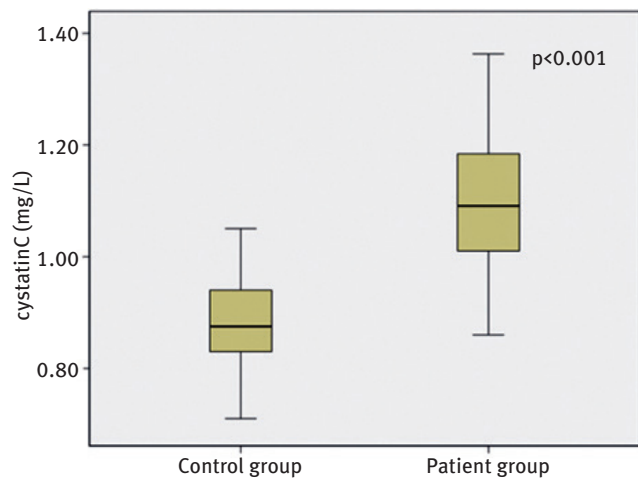
Figure 1: Comparison of cystatin C levels between groups.

Discussion

In the evaluation of renal functions, GFR has a vital importance and endogenous or exogenous substances can be used in its calculation. As exogenous substances are more expensive and not practical in application, endogenous substances are preferably used in the calculation of GFR, especially in children [10–15]. While acute and high level exposure to toxic metals causes acute GFR changes, chronic and low level exposures can lead to mild clinical manifestations, which is really obscure that can prevent the accurate diagnosis. In these conditions, Cyctatin C seems to be a better and more sensitive biomarker than creatinine [16–18].

In some studies it is emphasized that cystatin C increases before creatinine in subclinical renal disease or in acute renal damage and for this reason cystatin C is important to assess renal functions and in terms of early diagnosis [21–24]. Peco-Antić A and collaborates stated that cystatin C was a reliable early marker to determine acute renal damage after cardiac surgery in a study that they had made with pediatric populations [25]. Treiber M and collaborates stated that cystatin C was a better marker than creatinine in neonatals to determine acute renal damage after perinatal hypoxia/asphyxia [26]. Similar results were found in animal experiments and also in the studies which were made with adults [27,28]. There are very few articles which assess renal functions in children who are exposed to acute mercury. The studies were mainly about dental amalgam fillings which cause low dose mercury exposure. In some of these studies, it was stated that low dose mercury exposure did not affect renal functions while the others stated that renal functions were impaired dose dependently [29,30]. In our study, we found

Table 3: Subgroup analysis of the exposed group according to the different levels of mercury.

	Control group (n=30)	Group 1 (n=18)	Group 2 (n=12)	Group 3 (n=9)	P value
Mercury (ug/L)	3.90 (0.02–6.08)	11.15 (10.50–18.60)	23 (20.3–28.4)	38.75 (30.2–57)	<0.001[a,b,c,d,e,f]
Creatinine (mg/dL)	0.60 (0.40–0.70)	0.55 (0.40–0.70)	0.50 (0.40–0.60)	0.50 (0.40–0.60)	0.884
Urea (mg/dL)	23.54 (19.26–38.52)	27.82 (19.26–34.24)	25.68 (19.26–38.52)	27.82 (17.12–47.08)	0.665
Cystatin C (mg/L)	0.89±0.13	1.1±0.12	1.1±0.13	1.07±0.1	<0.001[a,b,c]
GFRshw1 (mL/min/1.73m²)	162.24 (126–214)	166.5 (124–221)	171.2 (142–221)	168 (132–214)	0.334
GFRcou (mL/min/1.73m²)	118.25 (98–165)	121.33 (96–161.7)	129.20 (111–163)	131.5 (103–165)	0.716
GFRfill (mL/min/1.73m²)	107.14±14.57	82.73±10.9	82.50±9.5	86.50±16.8	<0.001[a,b,c]
GFRzapp (mL/min/1.73m²)	106.61±12.27	92.48±13.71	93.39±9.06	96.30±10.4	0.001[a,b,c]
GFRshw2 (mL/min/1.73m²)	103.78±11.83	98.43±10.43	99.02±7.7	99.56±10.5	0.242
GFRkdigo1 (mL/dk/1.73m²)	113 (94–158)	116 (92–155)	123 (106–156)	126 (99–159)	0.762
GFRkdigo2 (mL/dk/1.73m²)	96.49±11.97	95.55±10.79	96.85±10.23	97.08±10.93	0.984
GFRkdigo3 (mL/dk/1.73m2)	79.43±9.6	64.86±7.09	64.32±6.24	68.43±6.40	<0.001[a,b,c]

The data are given as median (25th-75th percentiles) or Mean±SD. [a]: Significant between control group and group 1; [b]: Significant between control group and group 2; [c]: Significant between control group and group 3; [d]: Significant between group 1 and group 2; [e]: Significant between group 1 and group 3; [f]: Significant between group 2 and group 3.

cystatin C levels significantly higher in patient group than control group in children with acute mercury exposure when creatinine levels were normal (p<0.001) Therefore we consider cystatin C level as a better marker than creatinine to assess renal functions in rapid GFR decreases due to acute exposures. We couldn't compare our results with other studies because we could not find a study which investigated renal functions and cystatin C levels in chidren who exposed to acute and high dose mercury.

Formulas based on different parameters are used to calculate GFR value accurately [13,14]. Formulas are generated to calculate GFR using serum creatinine and/or cystatin C concentrations, in children. Formulas of Schwartz, Counahan, Filler, Zappitelli and collaborates [19] may be given as an example to this. Also, KDIGO 2012 Clinical Practice Guideline has suggested three pediatric GFR estimating equations [20]. Most commonly used formula for GFR calculation in children is GFRshw1 formula which Schwartz and collaborates generated using height and serum creatinine values. Given in Table 1, GFRshw1, GFRcou and GFRkdigo1 equations are based on serum creatinine and height, GFRkdigo2 equation is based on serum creatinine, height and urea, GFRfill, GFRzapp, GFRshw2 and GFRkdigo3 equations are formulas using only cystatin C or using parameters like creatinine, height, urea additionally cystatin C.

In GFR calculations with GFRfill, GFRzapp, GFRshw2 and GFRkdigo3 equations, a significant difference was detected between results of control and patient groups (p<0.001, p<0.001, p=0.042, p<0.001, respectively). In GFR calculations with GFRshw1, GFRcou, GFRkdigo1 and GFRkdigo2 equations, there was not a significant difference between results of control and patient groups (p=0.069, p=0.559, p=0.424, p=0.945, respectively).

Different results were obtained in studies which renal functions were evaluated with different GFR formulas. Nehus EJ and collaborates stated that in their study with pediatric patients, GFR results which uses only cystatin C were more accurate than both cystatin C and creatinine based GFR results [31]. In another study with pediatric patients, Westland R. and collaborates emphasized that creatinine and cystatin C based GFR results were more reliable than formulas based only creatinine or cystatin C [32]. There were reported different aspects also in studies with adults [33,34]. In some of the studies that compared creatinine and cystatin C based GFR results with each other and which reported that cystatin C based GFR formulas were significantly different from control group, it was also stated that creatinine based GFR results were higher than cystatin C based GFR results [35]. Also in our study, when cystatin C based GFR results were significantly different

from control group, there was no significant difference in terms of creatinine based GFR results in the mercury exposured group (Table 2). In our best knowledge, while there was no significant difference between control and patient groups in terms of creatinine level, there was a significant difference in terms of cystatin C level. In our study, we also found that creatinine and height based GFR results were higher than cystatin C based GFR results. For this reason, according to this study's results in rapid or mild GFR decreases, cystatin C based GFR formulas can provide more reliable results than creatinine based GFR formulas and we believe that more comprehensive researches about this issue should be done.

In subgroup analysis, cystatin C values were found to be higher than the control group , GFRfill, GFRzapp and GFRkdigo3 values were found to be lower than the control group (p<0.001, <0.001, p=0.001, p<0.001, respectively), however, there was not a significant difference between the subgroups (Table 3). It represented that these parameters were affected from mercury exposure but this effect was independent from the grade of exposure. Although mean GFRshw2 values were found higher in control group than in subgroups, there wasn't a significant difference between them. We think that it was resulted from the number of sample.

As a conclusion we consider that cystatin C is a better marker than creatinine and cystatin C based formulas are more effective than creatinine based formulas in rapid GFR decreases like acute intoxications. The data on this area is limited and we believe that our findings are useful for further researchs, especially on children with acute renal damage. Furthermore in our opinion it is important to evaluate data of adults who have been exposed to metal as well.

Ethical Considerations: The study was approved by the Ethical Committee of Ankara Numune Education and Research Hospital. The date and number of the permission were 23/01/2013 and 2013-517 respectively.

Conflict of Interest: The authors have no conflict of interest.

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