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Comparison of three different creatinine clearance calculation methods in patients with type 2 diabetes mellitus

Tip 2 diyabetik bireylerde kreatinin klirensini hesaplamada kullanılan üç farklı yöntemin karşılaştırılması

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Abstract

Aim: To determine the most accurate and useful method for calculating creatinine clearance by comparing the results of different methods.

Methods: Type 2 Diabetic 100 patients who have been followed by Okmeydani Training and Research Hospital internal medicine and/or diabetes policlinics. Individuals with Type 1 Diabetes Mellitus and acute kidney disease were excluded from the study.

Results: Glomerular filtration rate calculated with Cockroft-Gault formula was significantly affected by creatinine, weight and age ($p<0.05$ for all) in a univariate model. In a multivariate model this was significantly independently affected by creatinine, weight and age ($p<0.05$ for all). Glomerular filtration rate measured with Modification of Diet in Renal Disease formula was significantly affected by creatinine and age ($p<0.05$ for all) and in a univariate model. In a multivariate model this was significantly independently affected by creatinine ($p<0.05$). Glomerular filtration rate measured with 24h urine was significantly affected by creatinine, weight and age ($p<0.05$ for all). In a multivariate model this was significantly independently affected by weight ($p<0.05$).

Conclusion: In this study, those three methods were similar and positively correlated to each other. Such findings prove that those three different methods are compatible with each other at glomerular filtration calculation and they are all useful in clinical practice. Practical and accurately intensive follow up of those patients will give a chance of better understanding this process and will help us with intervention as soon as possible when needed.

Keywords: Glomerular filtration rate, Cockroft-Gault, MDRD, creatinine clearance.

Öz

Amaç: Diyabetik bireyler için kullanılabilecek en uygun kreatinin klirensi hesaplama metodunu belirlemek amaçlandı.

Yöntem: Çalışmaya Okmeydanı Eğitim Araştırma Hastanesi iç hastalıkları ve diyabet polikliniklerine başvurmuş 100 tip 2 diyabetik hasta dahil edildi. Tip 1 diyabet, hipertansiyon ve akut böbrek yetersizliği tanısı almış diyabetik hastalar çalışma dışı bırakıldı.

Bulgular: Cockroft-Gault değerini kestirmede tek değişkenli modelde yaş, ağırlık, kreatininin anlamlı (hepsi için $p<0,05$) etkisi gözlenmiştir. Çok değişkenli modelde ise yaş, ağırlık, kreatinin değerinin anlamlı bağımsız (hepsi için $p<0,05$) etkisi gözlenmiştir.

MDRD değerini kestirmede tek değişkenli modelde yaş, kreatininin anlamlı ($p<0,05$) etkisi gözlenmiştir. Çok değişkenli modelde ise kreatinin değerinin anlamlı bağımsız ($p<0,05$) etkisi gözlenmiştir.

24 saatlik idrarda kreatinin klirensi değerini kestirmede tek değişkenli modelde yaş, ağırlık, kreatinin değerinin anlamlı (hepsi için $p<0,05$) etkisi gözlenmiştir. Çok değişkenli modelde ise ağırlık değerinin anlamlı bağımsız ($p<0,05$) etkisi gözlenmiştir.

Sonuç: Bu çalışmada, bu üç yöntem birbirleriyle pozitif korelasyon gösterdi. Bundan yola çıkarak klinik pratikte her üç metodun da kullanılabileceği söylenebilir. Bu hastaların yakından düzenli takibi bu sürecin daha iyi anlaşılmasını sağlayacağı gibi bizlere de ihtiyaç olduğunda erken müdahale imkanı sunar.

Anahtar kelimeler: Glomerular filtrasyon hızı, Cockroft-Gault, MDRD, kreatinin klirensi

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Introduction

Diabetes mellitus (DM) is a chronical and progressive disease. Approximately 150 million people are suffering from this disease and predicted the number for 2025 is 300 million [1, 2].

Morbidity and mortality due to DM and its complications are increasing as the prevalence of type II DM increases [3]. Consequently, early diagnosis and effective treatment of type II DM is needed more and more every day. There are approximately 2.6 million type II DM patients in our country, and it is predicted that at least one-third of 1.8 million people still in impaired glucose tolerance stage will join to this group in the near future [4].

Diabetic nephropathy (DN) is a serious health problem causing end-stage renal failure. In the United States of America, DN causes 40 % of newly developed end-stage renal failure. DN defined as positive urine albumin stick test or excretion of albumin more than 300 mg in a diabetic patient who is not suffering from other renal diseases. DN, as appears a late finding of diabetes has some physiological, pathological and clinical symptoms. That made some researchers consider DN into stages [5].

Creatinine clearance measurement is the most common method for evaluating renal functions. Creatinine clearance may be measured with 24-hour urine collection and also with Cockcroft-Gault formula and MDRD.

In this study, we aimed to to determine the most accurate and useful method for calculating creatinine clearance by comparing the results of different methods. It was aimed to improve feasibility by determining the most suitable method to be possible.

Material and methods

This retrospective study approved by Okmeydani Training and Research Hospital Clinical Research Ethical Board Presidency with a number of 178 at 09.09.2014. Files of type 2 DM patients who applied to one of internal medicine outpatient clinics between 2012 and 2014 were retrospectively screened. From a total of 184 patients; patients with hypertension (n=74), acute renal failure (n=6) or renal transplantion (n=4) were excluded from the study. The remaining 100 patients (56 female, 44 male) included to the case group. Median age of the patients was 56 years with a range from 20 to 82 years.

Patients' characteristics (age, gender and weight (kilograms)) and laboratory findings (serum creatinine level (mg/dl), fasting blood glucose (mg/dl), postprandial blood glucose (mg/dl), HbA1c (%) and 24-hour urine creatinine clearance (GFR24) (mg/24 hours)) were evaluated. Roche-Hitachi Cobas 8000 (Serial number: 1349-09, 2014, Japan) was used to evaluate laboratory findings. The prediction of creatinine clearance (in ml/min) by the Cockcroft-Gault formula (GFRC&G) was calculated as (140 − age) × body weight/plasma creatinine × 72 (× 0.85 if female) [6]. The abbreviated MDRD (GFRMDRD) estimate of the kidney function was calculated as 175 × plasma creatinine−1.154 × age−0.203 (× 0.742 if female) [7]. Grading of the patients with regard to renal failure were performed according to the KDIGO 2017 guideline using GFR values (G1-G5) (Table 1) [8].

Statistical analysis

IBM SPSS for Windows 21.0 (Armonk, New York, USA) statistics package program was used. Mean, median, minimum, maximum, frequency values and standard deviation were used for defining statistics of data. Distribution of the variables was controlled with Kolmogorov Simirnov test. Unpaired t-test and Mann-Whitney U test were used for quantitative data analysis. Chi-square test was used for qualitative data analysis. Spearman correlation test was used for correlation analysis. Univariate and multivariate regression tests were performed. Level of significance was determined as $p \leq 0.050$ for all.

Table 1. Glomerular filtration rate categories in chronic renal failure*.

GFR category	GFR (ml/min/1.73m^2)
G1	≥ 90
G2	60 - 89
G3a	45 - 59
G3b	30 - 44
G4	15 – 29
G5	< 15

* In the absence of evidence of kidney damage, neither category G1 nor G2 fulfill the criteria for chronic renal failure.

Results

A total of 100 patients were staged by GFR. Sixty-nine patients (69%) had GFR greater than 90 mL/min. staged as G1, 22 patients (22%) had GFR between 60-89 mL/min staged as G2 and 9 patients (9%) had GFR between 30-59 mL/min staged as G3. None of the patients staged as G4 and G5.

Creatinine clearance of the patients was calculated by Cockcroft-Gault formula (GFRC&G), Modification of Diet in Renal Disease (GFRMDRD) and 24h urine collection method (GFR24). Mean values of these three methods were 96.4±28.8 mL/min, 104.5±29.8 mL/min and 86.2±24.7 mL/min for GFR24, GFRC&G and GFRMDRD, respectively.

Table 2 shows statistical values of patients' in terms of gender, weight, fasting blood glucose, postprandial blood glucose, HbA1c, GFR24, GFRC&G and GFRMDRD (Table 2).

Table 2. Characteristic features of the patients.

Variable	
Age (years)¥	56.1±10.2
Genderβ	
Female	56 (56)
Male	44 (44)
Weight (kg)¥	84.5±14
Creatinine (mg/dL)¥	0.9±0.3
Fasting blood glucose (mg/dL)¥	175.7±64.7
Postprandial blood glucose (mg/dL)¥	258.3±97.4
HbA1c (%)¥	8.2±1.8
Cockcroft-Gault (mL/min)¥	104.5±29.8
MDRD (mL/min/1.73m^2)¥	86.2±24.7
Creatinine Clearance with 24h urine (mL/min)¥	96.4±28.8

¥: mean±standard deviation, β:n (%)

Significant ($p<0.050$ for all) negative correlation was observed between creatinine levels and GFRC&G, GFRMDRD, GFR24. Significant ($p<0.050$ for all) positive correlation was observed between GFRC&G, GFRMDRD and GFR24. Significant ($p<0.050$ for all) positive correlation revealed between fasting blood glucose, postprandial blood glucose and HbA1c (Table 3).

In both univariate and multivariate models age, weight, and creatinine had significant ($p<0.050$ for all) association on determining GFRC&G value (Table 4). Although in a univariate model age and creatinine had significant ($p<0.050$ for all)

association on determining GFRMDRD value; in a multivariate model only creatinine had independently significant (p=0.001) association (Table 5). Although in a univariate model age, weight and creatinine had significant (p<0.050 for all) association on determining GFR24 value; in a multivariate model only weight had independently significant (p=0.001) association on determining GFR24 value (Table 6).

		Creatinine (mg/dL)	Fasting blood glucose (mg/dL)	Post prandial blood glucose (mg/dL)	HbA1c (%)	Cockcroft-Gault (mL/min)	MDRD (mL/min/ 1.73m^2)
Fasting Blood Glucose (mg/dL)	r	0.145					
	p	0.149					
Postprandial Blood Glucose (mg/dL)	r	0.096	0.633				
	p	0.340	0.001				
HbA1c (%)	r	0.081	0.702	0.504			
	p	0.423	0.001	0.000			
Cockcroft-Gault (mL/min)	r	-0.373	0.086	-0.004	0.187		
	p	0.001	0.392	0.968	0.062		
MDRD (mL/min/1.73m^2)	r	-0.592	-0.111	-0.109	-0.029	0.660	
	p	0.001	0.273	0.280	0.775	0.001	
Creatinine Clearance with 24h urine (mL/min)	r	-0.399	-0.137	-0.135	-0.057	0.679	0.627
	p	0.001	0.175	0.181	0.572	0.001	0.001

Table 3: Correlations with different methods calculating glomerular filtration rate.

Cockcroft-Gault	Univariate model				Multivariate model			
	β	95.0% CI		p	β	95.0% CI		p
		Low	High			Low	High	
Age (years)	-1.74	-2.21	-1.28	0.001	-1.08	-1.24	-0.9	0.001
Gender	10.69	-1.09	22.46	0.075				
Weight (kg)	1.19	0.84	1.54	0.001	1.12	1.00	1.23	0.001
Creatinine (mg/dL)	-51.8	-67.00	-36.77	0.001	-35.12	-41.74	-28.50	0.001
Fasting glucose (mg/dL)	0.00	-0.09	0.10	0.931				
Postprandial glucose (mg/dL)	0.00	-0.06	0.06	0.984				
HbA1c (%)	2.03	-1.20	5.25	0.215				

Table 4: Evaluation of the Cockroft-Gault method by linear regression.

MDRD	Univariate model				Multivariate model			
	β	95.0% CI		p	β	95.0% CI		p
		Low	High			Low	High	
Age(years)	-0.91	-1.36	-0.46	0.001				
Gender	9.61	-0.14	19.36	0.053				
Weight(kg)	0.18	-0.17	0.53	0.311				
Creatinine (mg/dL)	-49.92	-61.4	-38.43	0.001	-26.20	-37.01	-15.4	0.001
Fasting glucose (mg/dL)	-0.06	-0.14	0.01	0.111				
Postprandial glucose (mg/dL)	-0.03	-0.08	0.02	0.237				
HbA1c (%)	-0.37	-3.07	2.32	0.784				

Table5. Evaluation of the MDRD method by linear regression.

Discussion

The incidence of DN is increasing in proportion to DM incidence and increased lifetime in diabetics. Our study showed that 73% of patients had GFR under 120 mL/min. However, in our study, there was no significant correlation between fasting blood glucose, postprandial blood glucose and HbA1c and GFR values measured by three different methods.

24h urine creatinine clearance	Univariate Model				Multivariate Model			
	β	95.0% CI		p	β	95.0% CI		p
		Low	High			Low	High	
Age (years)	-1.02	-1.54	-0.49	0.001				
Gender	8.74	-2.69	20.16	0.133				
Weight (kg)	0.82	0.44	1.20	0.001	0.42	0.06	0.8	0.024
Creatinine (mg/dL)	-40.02	-55.82	-24.21	0.001				
Fasting glucose (mg/dL)	-0.08	-0.17	0.01	0.080				
Postprandial glucose (mg/dL)	-0.04	-0.10	0.02	0.199				
HbA1c (%)	-1.09	-4.22	2.04	0.491				

Table 6. Evaluation of 24h urine creatinine clearance method by linear regression.

This study compared the most popular three methods for calculating creatinine clearance. One of those methods, Cockcroft & Gault formulation uses serum creatinine, age, weight, and gender to calculate creatinine clearance by the unit ml/min [6].The second one is MDRD formulation uses race, age, serum creatinine and gender [7]. The last method is to evaluate the creatinine level in urine patient collected for 24 hours without interruption.

A study compared Cockcroft & Gault formulation, and MDRD formulation suggested that Cockcroft & Gault formulation calculated the lowest creatinine clearance in patients above age 70; while MDRD formulation is the most valuable method to estimate mortality rate in patients above age 85 [9]. In this study, the median age was under 70. GFRMDRD was slightly lower than GFRC&G without statistical signification. Yet another study published in 2007 suggested that Cockcroft&Gault formulation achieved more accurate results than other methods [10]. Another study published in 2010 suggested that Cockcroft&Gault formulation is superior to the MDRD formulation in patients with normal creatinine clearance and diabetics with normal or close to normal GFR. Otherwise, MDRD formulation has had more accurate results [11].

Our study revealed serum creatinine levels are increasing with age. Yet increased age resulted with lower GFRC&G, GFRMDRD, and GFR24h. Those results pointed out that age may be a prognostic factor for diabetic nephropathy. A study published at 2002 including 98.688 patients age between 20 and 94 years showed progressively increasing serum creatinine levels in male patients from age 60 and female patients from age 40 [12]; results of our study are consistent with this study.

In our study, independent factors that significantly affected GFRC&G increase are age, weight and serum creatinine. This result was expected as they all are variables in the Cockroft-Gault formulation. This result is consistent with the findings of two other studies. [13, 14]; and being in association with weight, is seemed to be the weakness of Cockroft-Gault formulation. Because of this deficit, another study recommended of estimating a CrCl range with the lower boundary defined by using ideal body weight in the Cockcroft-Gault equation and the upper boundary by using total body weight [15].

Independent factors significantly affected GFRMDRD increase are age and serum creatinine. This is consistent with the

previous studies [13, 16]. This result was expected as they are also variables in the MDRD formulation. It is not surprising that there is no effect of weight on the GFRMDRD since the MDRD formula does not use weight.

Independent factors significantly affected GFR24h increase are age, weight, and serum creatinine. As creatinine is released from the muscles and muscles are the big part of our weight; weight should be considered normal to affect the GFR24h.

An increase in GFR24h had a positive correlation with GFRMDRD and GFRC&G. This result indicated these three methods are consistent among themselves.

Major limitations of this study are being retrospective and the small sample size: Because of the retrospective design of the study some important clinical features could not be recorded. The small sample size may have limited our ability to detect statistically significant results.

In conclusion, there was no statistically significant difference between Cockcroft-Gault formulation, MDRD formulation and creatinine clearance with 24 hours urine method; they are all equally useful in clinical practice. So all of three methods can be used for evaluating renal functions in Type II diabetic patients but creatinine clearance with 24 hours urine method requires two patient visits in a row and a more complex biochemistry laboratory, and it might give incorrect results because of lack of communication between physician-patient-laboratory triangles especially in an outpatient clinic. In our opinion, this method may remain in the background because of the process.

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