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Filename	Chapter 2 Estimation of the glomerular filtration rate in patients with diabetes mellitus type 2 from plasma creatinine concentration after cimetidine administration

SOURCE (OR PART OF THE FOLLOWING SOURCE):

Type	Dissertation
Title	Improvements in the use of plasma creatine as a marker of the glomerular filtration rate
Author	F.A.W. Kemperman
Faculty	Faculty of Medicine
Year	2001
Pages	151
ISBN	909015051X

FULL BIBLIOGRAPHIC DETAILS:
http://dare.uva.nl/record/91636

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Chapter 2

Estimation of the glomerular filtration rate in patients with diabetes mellitus type 2 from plasma creatinine concentration after cimetidine administration

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Diabetes Care 1998;21:216-220

Abstract

Background: The glomerular filtration rate (GFR) can be estimated in patients with renal disease from plasma creatinine concentration, age, gender and body weight, according to the formula of Cockcroft and Gault. The hypothesis that this method can be improved when tubular secretion of creatinine is inhibited by cimetidine was studied in patients with diabetes mellitus type 2.

Methods: In 30 outpatients with normo- (n=10), micro- (9) or macroalbuminuria (11) GFR was measured as the urinary clearance during continuous infusion of ^{125}I-iothalamate. Plasma creatinine concentration was analyzed with an enzymatic assay before and after oral cimetidine 800 mg t.i.d. during 24 hours.

Results: Plasma creatinine rose in all patients after cimetidine administration and as a consequence the GFR estimated from the formula of Cockcroft and Gault (CG) fell. The ratio CG/GFR decreased from 1.16 ± 0.20 (mean ± standard deviation) to 0.97 ± 0.16. This ratio tended to be smaller in the normo- (0.93) than in the micro- (0.98) and macroalbuminuric group (1.00). Also 20 patients with a BMI <30 kg/m^2 had a smaller ratio (0.92) than those with a BMI >30 (1.07, $P<0.05$). Bland and Altman analysis showed a difference of CG and GFR of 12.0 ± 17.4 ml/min/1.73m^2 which decreased to -3.8 ± 14.8 ml/min/1.73m^2. The same analysis of the endogenous creatinine clearance with urine collection and GFR showed larger standard deviations.

Conclusion: GFR can be estimated in an acceptable way from the plasma creatinine concentration after cimetidine administration in outpatients with diabetes mellitus type 2. Despite a nonsignificant underestimation in normoalbuminuric and overestimation in overweighted patients this method is superior to the endogenous creatinine clearance with outpatient urine collection.

Introduction

The assessment of glomerular filtration rate (GFR) in diabetes mellitus type 2 is of importance in clinical management and intervention studies. Some investigators have used radio-isotope labelled filtration markers in follow up studies, but this is hardly feasible in daily practice. One of the major drawbacks in the use of creatinine as a marker of GFR is the variable amount of creatinine secreted in the proximal tubule. This may cause an unpredictable overestimation of GFR, sometimes as high as 100 % or more [1,2]. Tubular secretion can be blocked by cimetidine, because this drug inhibits competitively the cation transport in the proximal tubular luminal membrane [3,4]. Consequently, the endogenous creatinine clearance after administration of cimetidine is a more accurate approximation of GFR that can be used in clinical medicine [5-7].

In order to circumvent the difficulty and inaccuracy of urine collections, Cockcroft and Gault have developed a formula to assess the creatinine clearance from the plasma creatinine concentration, age, gender and body weight [8]. After administration of cimetidine the formula provided an accurate estimation of GFR in patients with a mild to moderate decrease in renal function due to various nephropathies and without important overweight [9]. However it is not clear whether this formula can be applied in patients with diabetes mellitus type 2, because obesity is present in 50-90% of these patients [10]. This causes an altered relationship between weight and muscle mass which may interfere with the accuracy of the Cockcroft-Gault formula. Alternatively, the endogenous creatinine clearance based on urine collection may also be inaccurate due to possible autonomic neuropathy of the bladder in this patient group.

To determine the most accurate estimation of GFR in outpatients with type 2 diabetes mellitus, we compared GFR to GFR-estimates from the Cockcroft-Gault formula or from the endogenous creatinine clearance, before and after the administration of cimetidine.

Material and Methods

Study population

Thirty outpatients of a mixed ethnic group with diabetes mellitus type 2 gave informed consent to participate in this study. Inclusion criteria were: plasma creatinine < 180 μmol/l, as we have previously shown that below 180 μmol/l plasma creatinine reaches a new steady state after inhibition of tubular secretion by cimetidine during 24 hours [9]. Other inclusion criteria were age <70 years because of possible inconvenience during the 5-day study and body mass index <35

kg/m² in the absence of edema, because important excess of fluid or fat increases the inaccuracy of the Cockcroft-Gault formula. None of the patients had jaundice as this interferes with the enzymatic creatinine analysis (see below). The patients were not allowed to take regular cimetidine, trimethoprim or salicylates, known to inhibit tubular creatinine secretion, during the study period and the preceding week. The patients were divided in three subgroups according to urinary albumin excretion (UAE): 10 patients with normoalbuminuria (UAE < 3 mg albumin/mmol creatinine), 9 with microalbuminuria (UAE 3-30 mg/mmol) and 11 with macroalbuminuria (UAE >30 mg/mmol). The patient characteristics are mentioned in Table 1.

Table 1 Characteristics (number, mean ± standard deviation or range) of 30 NIDDM-patients.

	normo-albuminuria	micro-albuminuria	macro-albuminuria
UAE (mg/mmol)	<3	3-30	>30
number of patients (♂/♀)	10 (6/4)	9 (4/5)	11 (8/3)
race (Ca/As/Af)	6/2/2	4/3/2	5/6/1
age (years)	52 (38-69)	50 (32-66)	58 (42-70)
diabetes duration (years)	8 (1-30)	7 (1-19)	11 (1-27)
patients with insulin therapy	6	6	5
patients with oral antidiabetics	3	3	3
patients with insulin + metformin	1	0	3
patients with antihypertensives	4	6	10
BMI (kg/m²)	27.5 ± 3.4	27.8 ± 4.0	28.5 ± 3.5
BP systolic (mm Hg)	131 ± 18	133 ± 13	146 ± 20
diastolic (mm Hg)	75 ± 9	80 ± 9	83 ± 10
HbA_{1c} (%)	7.7 ± 1.0	8.2 ± 1.6	9.0 ± 2.3

UAE: urinary albumin excretion (mg/mmol: mg albumin/mmol creatinine); Ca: caucasian, As: asian, Af: african; BP: blood pressure; HbA_{1c} reference value <6.7%. ANOVA did not detect significant differences between the 3 groups, with the exception of UAE.

Study protocol and laboratory methods

The study was performed on five consecutive days. On day 1 a plasma sample was drawn in the morning for creatinine determination; the 2nd, 3rd and 4th day patients were asked to collect three 24-hour urine samples starting at 8 a.m. They were instructed to take cimetidine 800 mg orally at 7 a.m., 3 p.m. and 11 p.m. on day 4 (total dose 2400 mg). The 5th day the patients

visited the outpatient clinic; fasting blood samples were drawn around 8 a.m. for analysis of creatinine, glucose and HbA_1c. From 9 a.m. to 3 p.m. the GFR was measured during continuous infusion of ^{125}I-iothalamate and ^{131}I-hippuran as described previously [9,11] and in the appendix of this thesis. The study protocol was approved by the committee of Medical Ethics of the Hospital Onze Lieve Vrouwe Gasthuis, Amsterdam.

Creatinine concentration in plasma was measured in duplicate with an enzymatic PAP (Phenol/4-AminoantiPyrine)-assay, in urine with the kinetic Jaffé reaction (Hitachi 747 and 717, Boehringer Mannheim, Germany). Urinary albumin analysis was performed with a nephelometer (BN-100, Hoechst-Behring, Marburg a/d Lahn, Germany). HbA_{1c} was analyzed with HPLC (Diamat, BioRad, Anaheim, California USA). Activities of radio-isotopes in plasma and urine were determined in duplicate with a gamma counter (Pharmacia type 1277, Wallac, Turku, Finland). GFR was calculated as the mean urinary clearance of ^{125}I-iothalamate of two 2-hour periods after a 2-hour equilibration period. Blood and urine samples were taken every 2 hours. Patients were seated and drank at least 200 ml every hour to maintain sufficient urine flow. In the GFR determination a correction is made for changes in plasma concentration, for instance due to the circadian rhythm of GFR, and for inaccuracies of urine collection during the GFR determination. This is based on the fact that urinary and plasma clearance of ^{131}I-hippuran are equal since there is no extrarenal clearance [11,12]. The Cockcroft-Gault formula was calculated before administration of cimetidine with the plasma creatinine concentration of day 1 and after cimetidine with that of day 5. The endogenous creatinine clearance was calculated before cimetidine administration using two 24-hour urine samples (day 2 and 3) and during cimetidine using one 24-hour urine sample (day 4). All clearances were corrected to a body surface area of 1.73 m^2 according to the DuBois-DuBois formula [13].

Statistical analysis

Data are expressed as means ± standard deviations (SD). ANOVA, with logarithmic transformation when appropriate, was used to study differences between subgroups of patients and the paired t-test for changes due to cimetidine administration in each subgroup. The agreement between GFR and either creatinine clearance or the Cockcroft-Gault formula was tested with Bland and Altman analysis [14]. The accuracy and variability are shown in this type of analysis by relating the difference between two methods in each patient to the mean of the same two methods in the same patient. It can also be analyzed whether a trendwise change in the

difference is present for increasing mean values. This method is preferred to correlation coefficients as it analyzes the agreement and not the relation between two methods. In a perfect correlation the points lie along any straight line, whereas in a perfect agreement the points lie along the line of equality. The variances of these agreements were compared with the method described by Armitage and Berry [15].

Table 2 Plasma creatinine concentration, GFR-estimates from the Cockcroft-Gault formula or the endogenous creatinine clearance and the glomerular filtration rate in 30 patients with NIDDM before and after administration of cimetidine 800 mg t.i.d. during one day (mean ± standard deviation).

	before cimetidine	after cimetidine
plasma creatinine (μmol/l)	78 ± 26	93 ± 30*
Cockcroft-Gault formula (ml/min/1.73 m^2)	101 ± 33	85 ± 30†
endogenous creatinine clearance (ml/min/1.73 m^2)	102 ± 40	86 ± 34‡
glomerular filtration rate (ml/min/1.73 m^2)	not done	89 ± 30

* the difference due to cimetidine administration was significant ($p < 0.001$).
† the difference due to cimetidine administration was significant ($p < 0.001$).
‡ the difference due to cimetidine administration was significant ($p < 0.005$).

Results

The results of plasma creatinine analysis, GFR-estimates from the Cockcroft-Gault formula or the endogenous creatinine clearance and the glomerular filtration rate determined as clearance of ^{125}I-iothalamate are shown in Table 2. GFR was normal in the normoalbuminuric group (105 ± 23 ml/min/1.73m^2) and reduced in the micro- (86 ± 28) and macroalbuminuric group (76 ± 32 ml/min/1.73 m^2). The effect of cimetidine on plasma creatinine concentration is illustrated in Figure 1. The increase tended to be most pronounced for the macroalbuminuric patients, but the differences between the three groups were not significant. The ratio of the GFR, estimated from the Cockcroft-Gault formula (CG), and the GFR determined with ^{125}I-iothalamate is shown in Figure 2. In all three groups an overestimation of GFR was observed before administration of cimetidine. After cimetidine the mean ratio decreased to 1.0 (macroalbuminuric group) or slightly below: 0.98 for the microalbuminuric and 0.93 for the normoalbuminuric group (N.S.). Ten

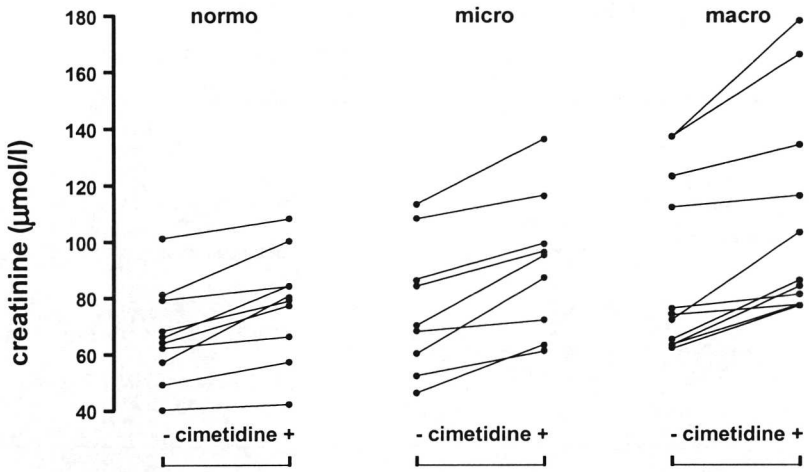

Figure 1 Plasma creatinine concentrations of 30 patients before and after cimetidine administration in the 3 subgroups (normo-, micro- and macroalbuminuria).

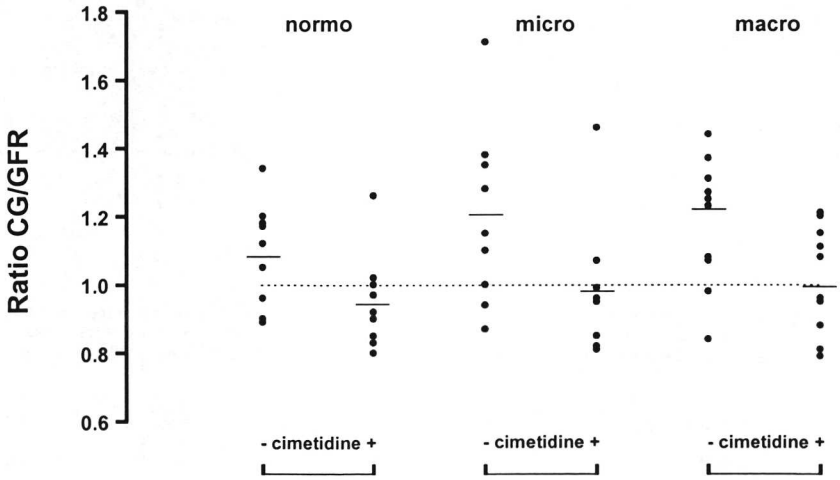

Figure 2 Ratio of the GFR, estimated from the Cockcroft-Gault formula (CG), and the GFR determined with ^{125}I-iothalamate of 30 patients before and after cimetidine in the 3 subgroups (normo-, micro- and macroalbuminuria). The horizontal lines indicate the mean ratio of each group.

patients were overweighted (BMI >30 kg/m^2). They had a higher ratio than the other 20 patients (1.07 ± 0.18 versus 0.92 ± 0.13, $P < 0.05$). This was partly due to one extreme overestimation (1.46 in the microalbuminuric group) in the patient with the highest BMI (33.6 kg/m^2).

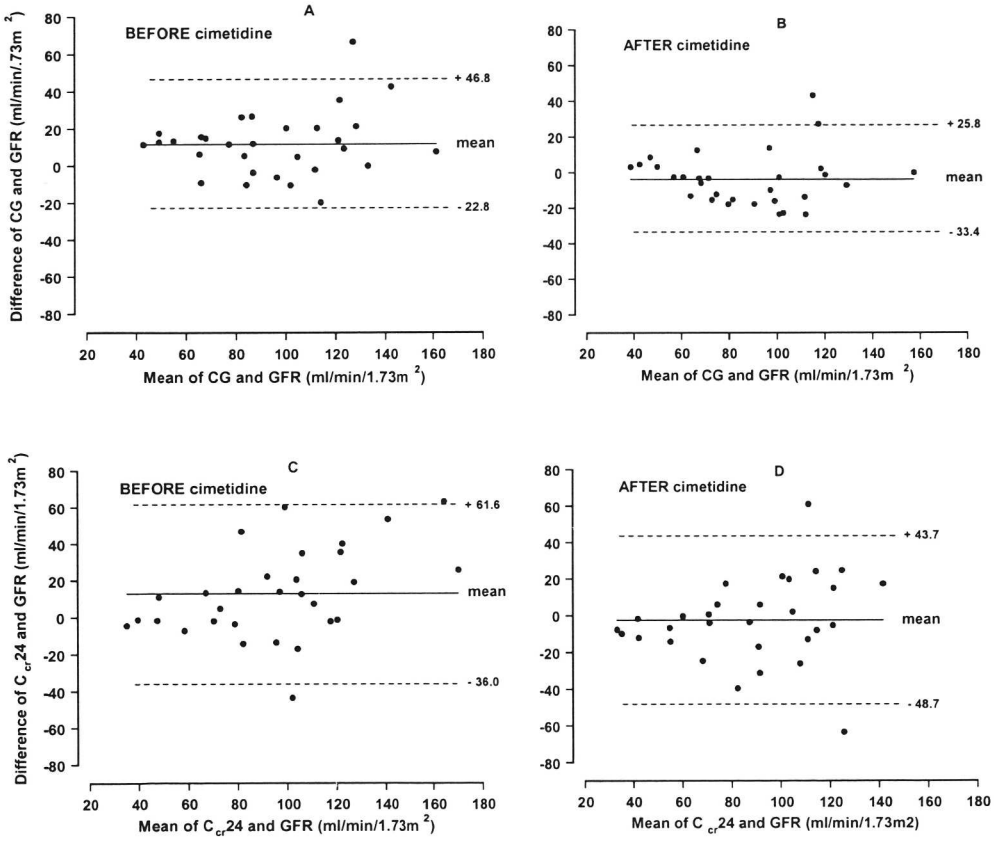

Figure 3 Analysis according to the method proposed by Bland and Altman of all 30 patients, which plot the difference against the mean of the ^{125}I-iothalamate GFR and its estimated value, namely the Cockcroft- Gault formula (CG) and endogenous creatinine clearance ($C_{cr}24$) before and after cimetidine. Panel A plots the difference against mean of CG and GFR before the administration of cimetidine. Panel B shows the same analysis for CG after cimetidine and GFR. Panel C plots the difference against mean of $C_{cr}24$ and GFR before the administration of cimetidine. Panel D shows the same analysis for $C_{cr}24$ after cimetidine and GFR.

The Bland and Altman analysis of GFR and its estimates from either the Cockcroft-Gault formula (CG) or from the endogenous creatinine clearance ($C_{cr}24$), both before and after cimetidine is shown in Figure 3. CG overestimated GFR by 12.0 ± 17.4 ml/min/1.73m^2. After cimetidine this overestimation changed to a slight underestimation of 3.8 ml/min/1.73m^2 and the variation (SD 14.8 versus 17.4 ml/min/1.73m^2 before cimetidine) tended to be smaller. The comparison of $C_{cr}24$ with GFR showed a mean overestimation of 12.8 ml/min/1.73m^2, which also decreased to an underestimation of 2.5 ml/min/1.73m^2. The difference of $C_{cr}24$ and GFR had a higher variation than that of CG and GFR (SD 24.4 versus 14.8 ml/min/1.73m^2, $P < 0.05$) and this remained high after cimetidine (SD 23.1 ml/min/1.73m^2).

Conclusions

The best approximation of GFR in this type 2 diabetic population was obtained by applying the formula of Cockcroft and Gault to the plasma creatinine concentration determined by the enzymatic PAP-assay after oral administration of cimetidine on the preceding day. This method proved to be better than three other approximations of GFR: (1) without administration of cimetidine there was an overestimation and the variation tended to be larger; (2) the endogenous creatinine clearance using 24-hour urine samples had a larger variation and (3) this was unchanged after cimetidine administration.

Other authors have reported an underestimation of GFR by the Cockcroft-Gault formula in patients with diabetes mellitus [16-18]. Gross et al. observed a 38% underestimation of GFR determined with a single shot ^{51}Cr-EDTA technique in patients with diabetes mellitus type 2 [16]. Idink-Mecking et al. also found a 13% underestimation of GFR, determined by continuous infusion of ^{125}I-iothalamate, in patients diabetes mellitus type 1 [17]. Zietse et al. described an underestimation of ^{125}I-iothalamate GFR by the formula of Cockcroft-Gault in type 1 diabetic patients with normal or elevated GFR [18].

There were 3 differences between these studies and the present study:

1. Cimetidine had not been given to inhibit tubular creatinine secretion, but this does not explain the difference as tubular secretion would have compensated part of the underestimation. 2. The use of a single shot radio-isotope tracer might be associated with an overestimation of GFR due to extrarenal clearance resulting in a too low ratio between the GFR-estimate from the Cockcroft-Gault formula and GFR. 3. The plasma creatinine analysis with the (modified) Jaffé

reaction is known for overestimating plasma creatinine because of non-creatinine chromogens or glucose interference; therefore, the GFR will be underestimated by the formula of Cockcroft and Gault as plasma creatinine is in the denominator.

In our study no important underestimation of GFR by the Cockcroft-Gault formula, using an enzymatic creatinine assay after inhibition of tubular secretion, was found. Only in the normoalbuminuric group, with the highest GFR, CG tended to be lower than GFR. This is partly in accordance with the results of the previous authors, because their patients had a normal or even elevated GFR and were normo- or microalbuminuric. In the subgroup of overweighted patients (BMI > 30 kg/m^2) the GFR-estimates from the Cockcroft-Gault formula were significantly higher than in the group with a BMI < 30. Apart from one extreme overestimation the Cockcroft-Gault formula after cimetidine estimated GFR quite well up to a BMI of 33.5 kg/m^2, and much better than the endogenous creatinine clearance did.

We found a mean overestimation of GFR by CG of 12.4 ml/min/1.73m^2, that changed into a slight underestimation of 3.8 ml/min/1.73m^2 after cimetidine. This implies a marked improvement of the accuracy of CG. The reduction in the SD (17.4 to 14.8 ml/min/1.73m^2) of the difference between CG and GFR was not significant. When patientgroups are compared this still influences the precision of the GFR estimations. However, the SD of the difference between CG and GFR is to a major extent due to the inappropriate reflection of muscle mass by weight. One might speculate that the precision of the Cockcroft-Gault formula after cimetidine would be much better when used for follow-up of individual patients.

In conclusion the formula of Cockcroft and Gault after cimetidine provides the clinician with an acceptable estimation of GFR that can be obtained in a feasible way in an outpatient type 2 diabetic population (up to a BMI of 33.5 kg/m^2), as it only requires a single bloodsample after one day of cimetidine administration.

Acknowledgements

We especially thank J.C. Kennedy for his dedicated radioisotope deteminations and GFR-calculations, E. Schipper for laboratory support, Dr. W. Lameijer for cimetidine analysis in urine, J. Oosting for statistical advice and the nurses of the outpatient clinic for much assistance.

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