Improvements in the use of plasma creatine as a marker of the glomerular filtration rate
Kemperman, F.A.W.

Citation for published version (APA):
Kemperman, F. A. W. (2001). Improvements in the use of plasma creatine as a marker of the glomerular filtration rate

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 3

Follow-up of GFR estimated from plasma creatinine after cimetidine administration in patients with diabetes mellitus type 2

Frits A.W. Kemperman\textsuperscript{1,4}, Joseph Silberbusch\textsuperscript{1}, Eduard H. Slaats\textsuperscript{2}, Ariël M. Prins\textsuperscript{3}, Raymond T. Krediet\textsuperscript{4}, Lambertus Arisz\textsuperscript{4}

Departments of Internal Medicine\textsuperscript{1}, Clinical Chemistry\textsuperscript{2}, Clinical Pharmacy and Radiopharmacy\textsuperscript{3} of the Hospital Onze Lieve Vrouwe Gasthuis, Amsterdam and Internal Medicine\textsuperscript{4} of the Academic Medical Centre, University of Amsterdam, The Netherlands

Background: The glomerular filtration rate (GFR) can be estimated from plasma creatinine according to the formula of Cockcroft and Gault (CG). When tubular secretion of creatinine is inhibited by cimetidine the mean difference between the Cockcroft-Gault formula (CG<sub>Gm</sub>) and GFR approximates zero, but there is still some interindividual difference, especially in type 2 diabetic patients. We studied during longitudinal follow-up, whether the discrepancies between CG<sub>Gm</sub> and GFR per patient are consistent in time in type 2 diabetic patients.

Methods: In 1996 and 1998 (interval 20 - 26 months) GFR was measured in 21 patients as the urinary clearance of continuously infused <sup>125</sup>I-iothalamate. Plasma creatinine was analyzed with an enzymatic assay before and after oral cimetidine 800 mg t.i.d. during 24 hours. GFR-estimations were calculated with the Cockcroft-Gault formula before (CG) and after cimetidine (CG<sub>Gm</sub>) and expressed as means ± SEM.

Results: GFR deteriorated from 89.7 ± 5.7 to 81.3 ± 5.8 ml/min/1.73 m<sup>2</sup> and CG<sub>Gm</sub> from 85.3 ± 5.7 to 81.1 ± 6.6 ml/min/1.73 m<sup>2</sup>, whereas CG decreased from 102.4 ± 6.8 to 98.4 ± 7.0 ml/min/1.73 m<sup>2</sup>. Changes in GFR and changes in CG<sub>Gm</sub> were correlated (r = 0.72, P < 0.001) and were not significantly different from each other. The discrepancy between CG<sub>Gm</sub> and GFR per patient in 1996 also correlated with the discrepancy between CG<sub>Gm</sub> and GFR in 1998 (r = 0.85, P < 0.001).

Conclusions: In individual patients the discrepancies between the CG<sub>Gm</sub> and GFR are consistent in time and the change in GFR is reflected by the change in CG<sub>Gm</sub>. This small variability means that CG<sub>Gm</sub>, based on an enzymatic plasma creatinine assay, would be suitable for follow-up of GFR in type 2 diabetic patients, independent of albuminuria.
Introduction

The degree of renal impairment in patients with type 2 diabetes mellitus is usually examined by determining urinary albumin excretion [1]. However, there is a potential for misleading conclusions when proxy markers of nephropathy progression are used and hard endpoints are needed such as a change in GFR or the incidence of end-stage renal disease [2]. Only recently it was shown that GFR was preserved by captopril in normotensive type 1 diabetic patients with microalbuminuria [3]. The usefulness of the plasma creatinine concentration - or its reciprocal value - for follow-up of GFR is limited because the contribution of tubular creatinine secretion increases when GFR deteriorates, thus keeping overall clearance fairly constant [4,5]. The same holds for the endogenous creatinine clearance based on an outpatient urine collections and for assessment of this clearance from plasma creatinine, age, weight and gender using the formula of Cockcroft and Gault (CG) [6-10].

Tubular secretion of creatinine can be inhibited by administration of cimetidine, which uses the same organic cation transporter in the proximal tubule but with much higher affinity [11], whereas this drug has no influence on GFR or renal plasma flow [12]. In an earlier study we have shown that in patients with a plasma creatinine concentration <180 μmol/l a new steady state of increased plasma creatinine is reached within 24 hours of cimetidine administration [13]. Using this approach the Cockcroft-Gault formula \((CG_{\text{cim}})\) was shown to give a good approximation of GFR in patients with various nephropathies and with type 2 diabetes at different stages of albuminuria [13,14]. It was also noticed that the application of an enzymatic creatinine assay was necessary for accurate GFR-estimation, compared to the alkaline picrate (Jaffé) method [15].

However, while there was a good accuracy of GFR-estimation in type 2 diabetic patients, the precision of GFR-estimation was found to be lower than in renal patients. We hypothesized that this was due to a larger variability in the relationship between body weight, used in the Cockcroft-Gault formula, and muscle mass than in non-diabetic patients. If the discrepancy between \(CG_{\text{cim}}\) and GFR is patient-specific and consistent in time, than any change in GFR would be reflected by a change in \(CG_{\text{cim}}\) provided that body mass index (BMI) and muscle mass remain constant [16]. The aim of the present study was therefore to investigate the usefulness of \(CG_{\text{cim}}\) for GFR-estimation during longitudinal follow-up in type 2 diabetic patients.
Material and Methods

Study population
We studied a cohort of 30 patients of mixed ethnic origin, aged 30-70 years with a plasma creatinine concentration < 180 \(\mu\)mol/l, equally distributed over a normo-, micro- and macroalbuminuric group; BMI was <35 kg/m\(^2\) in the absence of edema. The results of the initial evaluation have been published previously [14]. Two years later the same patients were asked to participate in a second assessment of GFR. This could be done in 21 of them, 20 to 26 months after the first investigation. Median age was 52 years (range 32 to 68), median BMI was 29 kg/m\(^2\) (22.5 to 34.2) and median change in BMI was 0.6 kg/m\(^2\) (-2.2 to +5.1). There were 12 male and 9 female patients. Nine were Caucasian, 7 Asian and 5 were African patients. During this study no patient had jaundice or used drugs known to interfere with tubular creatinine secretion.

Study protocol
The study was performed on three consecutive days. The patients collected 3 morning urine samples for calculation of the albumin/creatinine ratio. Plasma creatinine samples were drawn the 1st and 3rd day around 8:00 A.M. and the patients were instructed to take cimetidine 800 mg orally on the 2nd day at 7:00 A.M. and at 3:00 and 11:00 P.M. The 3rd day from 9:00 A.M. to 3:00 P.M. GFR and renal plasma flow was measured during continuous infusion of \(^{125}\)I-labeled iothalamate and \(^{131}\)I-labeled hippuran as described before [13,17]. 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 (Hitachi 747, Roche Diagnostics, Mannheim, Germany). GFR was calculated as the mean urinary clearance of \(^{125}\)I-iothalamate of two 2-hour periods after a 2-hour equilibration period as described before [13,17] and in the appendix of this thesis. GFR-estimations were calculated with the formula of Cockcroft and Gault:

\[
\text{GFR} = \frac{(140-\text{age}) \times \text{body weight}}{0.815 \times \text{plasma creatinine}}
\]

[for women correction factor 0.85; age in years, weight in kg, plasma creatinine in \(\mu\)mol/l].

58
Prior to administration of cimetidine this was done with the plasma creatinine concentration of day 1 (CG) and after cimetidine with the concentration of day 3 (CG$_{\text{cim}}$). All clearances were corrected for body surface area according to the DuBois-DuBois formula [18] and expressed as ml/min/1.73 m$^2$.

**Statistical analysis**

Data are expressed as means ± standard deviations (SD), unless stated otherwise. The paired t-test was used for comparison. Pearson’s correlation coefficients were calculated for comparison of discrepancies between and changes in GFR and CG$_{\text{cim}}$. The agreements between GFR and CG$_{\text{cim}}$ were tested with an analysis of agreement, as described by Bland and Altman [19]. The accuracy and precision of agreement 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. The limits of agreement can be expressed as mean + 2SD and mean - 2SD, in which 95% of the values are situated. A difference with $P < 0.05$ was considered to be significant.

**Results**

![Figure 1](image-url) The mean ± standard error of the Cockcroft-Gault clearance before (CG) and after cimetidine (CG$_{\text{cim}}$) and GFR of 21 type 2 diabetic patients in 1996 (♦) and 1998 ( ■). The values are 102.4 ± 6.8, 98.4 ± 7.0, 85.3 ± 5.7, 81.1 ± 6.6, 89.7 ± 5.7 and 81.3 ± 5.8 ml/min/1.73 m$^2$. 
Figure 2 The analysis of agreement in 21 patients. In this analysis the difference between two methods is plotted against their mean for each individual patient. This was done for the Cockcroft-Gault clearance after cimetidine (CG\textsubscript{Gm}) and GFR in 1996 (left panel) and in 1998 (right panel). Mean difference is indicated by a drawn line, the limits of agreement (mean - 2SD and mean +2SD) are indicated by the dashed lines.

The comparison between 1996 and 1998 for CG, CG\textsubscript{Gm} and GFR is shown in Figure 1. In both years CG overestimated GFR \((P < 0.001)\), whereas CG\textsubscript{Gm} did not. The decrease in mean GFR was 8.4 and in CG\textsubscript{Gm} 4.2 ml/min/1.73 m\(^2\). In 1998 GFR ranged from 27 to 139 ml/min/1.73 m\(^2\).

In Figure 2, the analysis of agreement demonstrated a discrepancy between CG\textsubscript{Gm} and GFR of -4.4 ± 15.1 ml/min/1.73 m\(^2\) in 1996 and -0.2 ± 18.4 ml/min/1.73 m\(^2\) in 1998 (N.S.). The difference between the change in GFR and the change in CG\textsubscript{Gm} was 4.2 ± 9.8 ml/min/1.73 m\(^2\) (N.S.). Figure 3 shows that the changes in GFR correlated well with the changes in CG\textsubscript{Gm} \((r = 0.72, P < 0.001)\). In only 3 cases the changes were discordant, i.e. GFR remained constant while CG\textsubscript{Gm} increased. The discrepancy between CG\textsubscript{Gm} and GFR per patient in 1996 also correlated with the discrepancy between CG\textsubscript{Gm} and GFR in 1998, as shown in Figure 4 \((r = 0.85, P < 0.001)\).
Follow-up of cimetidine aided GFR-estimation

**Figure 3** The change in GFR and the change in Cockcroft-Gault clearance after cimetidine (CG<sub>cam</sub>) of all 21 patients in relation to the line of identity. Negative values indicate a decrease between 1996 and 1998. The Pearson’s correlation coefficient was 0.72 (P < 0.001).

**Figure 4** The discrepancy of CG<sub>cam</sub> and GFR in 1996 and that of 1998 of all 21 patients in relation to the line of identity. Positive values indicate an overestimation of GFR by CG<sub>cam</sub>. The Pearson’s correlation coefficient was 0.85 (P < 0.001).

**Conclusions**

In this study it was analyzed whether the cimetidine aided GFR-estimation by the formula of Cockcroft and Gault (CG<sub>cam</sub>) might be a useful approach for the routine follow-up of renal function in type 2 diabetic patients. For this purpose we studied on two occasions with an interval of two years a group of patients with a BMI < 35 kg/m<sup>2</sup> and a plasma creatinine < 180 μmol/l. We used the urinary clearance of continuously infused <sup>125</sup>I-iothalamate as representing true GFR. We chose this patient group because weight, used in the numerator of the Cockcroft-Gault formula, overestimates muscle mass at higher BMI and then leads to inaccuracies in GFR-
estimation from the Cockcroft-Gault formula (CG). Furthermore the change in GFR is not accurately reflected by the plasma creatinine concentration or its reciprocal value in the range investigated [4,5]. The study shows that the accuracy and precision of the GFR-estimations from CG were the same on the two occasions. In individual patients the discrepancy between the CG and GFR appeared to be consistent in time. Also, the change in GFR was reflected by the change in CG. This indicates that CG is a simple and useful approach for the follow-up of renal function in type 2 diabetic patients at all stages of albuminuria.

Other studies have shown that follow-up of GFR by plasma creatinine with or without the CG-formula, the reciprocal value of plasma creatinine or timed urinary clearance is not accurate [5] [7-10]. These studies used an alkaline picrate method for determination of the plasma creatinine concentration. Shemesh et al. followed patients with deteriorating or improving renal function during treatment of glomerular disease [5]. They demonstrated large percentual differences between the change in GFR, measured with continuously infused inulin, and the change in simultaneously measured creatinine clearance, plasma creatinine and the reciprocal value of plasma creatinine. Nielsen et al. reported follow-up in type 2 diabetic patients with microalbuminuria and normal renal function [10]. GFR was measured by the plasma clearance of single shot $^{51}$Cr-EDTA and estimated by the CG-formula. The change in GFR did not correlate well with the change in CG-clearance ($r = 0.49$). They therefore considered the CG-formula of limited value. In an earlier study we have found major differences between plasma creatinine measurements using an alkaline picrate or an enzymatic plasma creatinine assay [15]. As a consequence, CG calculated with the alkaline picrate creatinine concentration was not appropriate for GFR-estimation. This makes it likely that the negative results of the previously published studies can be explained by the method of plasma creatinine determination used.

The most important advantage of the CG over GFR measurements is the convenience to obtain it as often as necessary during follow-up of patients. It is conceivable that our results can be extrapolated to non-diabetic patients as we have previously shown in a transversal study that in these patients GFR-estimation has the same accuracy and even a better precision [13]. We did not correct the decrease of GFR for changes due to aging, since the cause of a change in GFR was not the primary goal of our study. However, caution should be made in patients above the age of 70 years, who were excluded from this study. In an elderly patient group an underestimation of GFR by CG without cimetidine was reported [20].
In conclusion, during an interval of two years the discrepancies between $CG_{\text{Cm}}$ and GFR in individual patients are consistent and the change in GFR is reflected by the change in $CG_{\text{Cm}}$. This small variability means that GFR-estimation from the Cockcroft-Gault formula after one day of cimetidine administration would be suitable for follow-up of GFR in type 2 diabetic patients, independent of albuminuria, provided plasma creatinine is determined with an enzymatic assay and below 180 $\mu$mol/l and BMI is less than 35 kg/m².

Acknowledgements

We especially thank J.C. Kennedy for his dedicated radioisotope determinations and GFR-calculations, E. Schipper for laboratory support, A.A.M. Hart and F. Dekker for statistical advice and the nurses of the outpatient clinic for much assistance.
References


