IS ENDOGENOUS CREATININE CLEARANCE STILL A RELIABLE INDEX OF GLOMERULAR FILTRATION RATE IN DIABETIC PATIENTS?

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Three methods routinely used for estimation of renal function - plasma creatinine, endogenous creatinine clearance and estimation of endogenous creatinine clearance from plasma creatinine - are compared with the measurement of glomerular filtration rate based on a single injection of ^{51}Cr-EDTA, a technique that was standardized for this study in 20 healthy volunteers. The different creatinine methods were compared with the ^{51}Cr-EDTA method in 30 diabetic patients, resulting in 68 sets of data in which all four estimates were made simultaneously. Spearman's correlation values (r_s) for comparing the three creatinine methods with that of ^{51}Cr-EDTA were 0.74, 0.40 and 0.82 ($P<0.05$). It is suggested that the use of endogenous creatinine clearance to estimate the glomerular filtration rate (GFR) requires caution and the recognition of the limitations of the method, and that simpler techniques (serum creatinine or estimated endogenous creatinine clearance) are preferable in routine practice. GFR based on ^{51}Cr-EDTA injection is the method of choice for monitoring renal function in special situations such as renal transplantation and progressive nephropathies.

Key words: creatinine, glomerular filtration rate, diabetes mellitus, ^{51}Cr-EDTA.

For many years, endogenous creatinine clearance has been used as a parameter of renal function and was considered to be a better index than plasma urea, phosphorus or uric acid (1). Lately, however, many authors have stated that this is a rather inaccurate method (2-5). This inaccuracy is attributed to difficulties in collecting the urine correctly and to variations in urinary creatinine levels due to tubular secretion or ingestion of meat. These findings have led to the suggestion that only plasma creatinine should be used to evaluate glomerular filtration rate (GRF) (5).

The purpose of this paper is to present a standardization of a practical and precise technique for measuring GRF - the single-injection method using ^{51}Cr-EDTA (^{51}Cr-EDTA/GFR) - and to compare its effectiveness with that of three more commonly used methods - plasma creatinine, endogenous creatinine clearance (ECC) and the estimation of endogenous creatinine clearance from plasma creatinine (ECCe) - in diabetic individuals.

Seventeen females and 13 males with type I or type II diabetes mellitus, aged 23 to 75, with body weights within 20% of the ideal, were evaluated on different occasions, resulting in a total of 68 sets of four simultaneous measurements of the following parameters: plasma creatinine, 24-h urinary creatinine and ^{51}Cr-EDTA/GFR. Creatinine

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was measured by the technique of Chasson et al. (6), which is an automated reaction-rate method carried out using a CentrifiChem Auto-Analyzer^{R}. ECC was calculated by the classical equation: ECC = urinary creatinine concentration x urinary flow rate x (plasma creatinine concentration)$^{-1}$, corrected to a body surface area of 1.73 m^2. Plasma creatinine was used to estimate ECCe according to Cockroft and Gault (7): ECCe = (140 - age) x (kg body weight) x (72 x plasma creatinine concentration)$^{-1}$, with a 15% reduction for women and correction for body surface area. ^{51}Cr-EDTA washout curves for the calculation of GFR were obtained as described by Chantler and Barratt (8): a single bolus of 5.55 MBq ^{51}Cr-EDTA (Instituto de Pesquisas Energéticas e Nucleares, São Paulo, Brazil) is injected into the cubital vein of the forearm and plasma samples are taken from the opposite extremity 2, 3 and 4 h later for measurement in a standard gamma-counter. The activity of each sample (in log-cpm) is plotted against time to obtain a curve that can be fitted by a linear regression for a single exponential. This allows the calculation of GFR (corrected to 1.73 m^2) in a microcomputer. We have standardized this technique in our laboratory using 20 healthy volunteers, 10 males, 25 to 44 years old and 10 females, 26 to 40 years old; all were within 20% of their ideal body weight. The utility of plasma creatinine, EEC and ECCe as estimates of GFR was evaluated by comparing values obtained by each method with GFR obtained by ^{51}Cr-EDTA using Spearman's correlation coefficient (r_s). The significance of the correlation was assessed by the Student *t*-test, with a level of significance of 5%.

The results of ^{51}Cr-EDTA/GFR for the normal males and females were, respectively, 115.5 ± 11.1 and 113.2 ± 8.9 ml min^{-1} (1.72 m^2)$^{-1}$ (mean ± SD). Since these means did not differ significantly they were pooled, resulting in a range from 96.4 to 134.0 ml/min. The coefficient of variation of the pooled data was 5%. In the 30 diabetic patients, ^{51}Cr-EDTA/GFR was 116.2 ± 47.3, ECC was 96.2 ± 37.0 and ECCe was 95.4 ± 37.1 ml min^{-1} (1.73 m^2)$^{-1}$. The comparison of individual ^{51}Cr-EDTA/GFR values with those obtained at the same time from creatinine, ECC and ECCe resulted, respectively, in the following r_s values: 0.74, 0.40 and 0.82. All three correlations were significant at the 5% level. Figures 1 and 2 show the correlation graphics for ECC and ECCe against ^{51}Cr-EDTA/GFR.

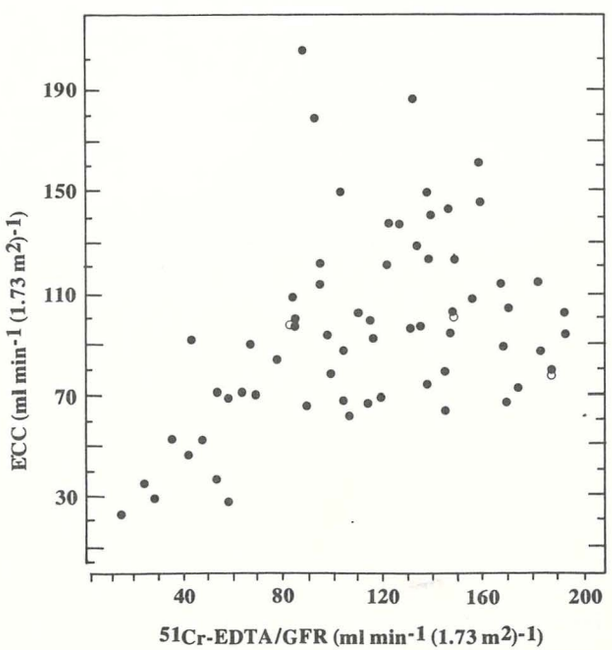

Figure 1 - Comparison of endogenous creatinine clearance (ECC) with glomerular filtration rate as measured by ^{51}Cr-EDTA (^{51}Cr-EDTA/GFR) in 30 diabetic patients. Spearman's correlation coefficient (r_s) was 0.40. P<0.05.

^{51}Cr-EDTA/GFR is considered to be a reliable method for measuring GFR, as it correlates very strongly with inulin clearance (1, 9). ^{51}Cr-EDTA is not metabolized, does not bind to plasma proteins and is excreted exclusively by the renal route, having the advantage of obviating urine collections (10). Our results comparing this technique with ECC confirm that ECC is an inaccurate method for estimating GFR. Although all three creatinine techniques were significantly correlated with ^{51}Cr-EDTA/GFR, the correlation was lowest for ECC, which was highly variable.

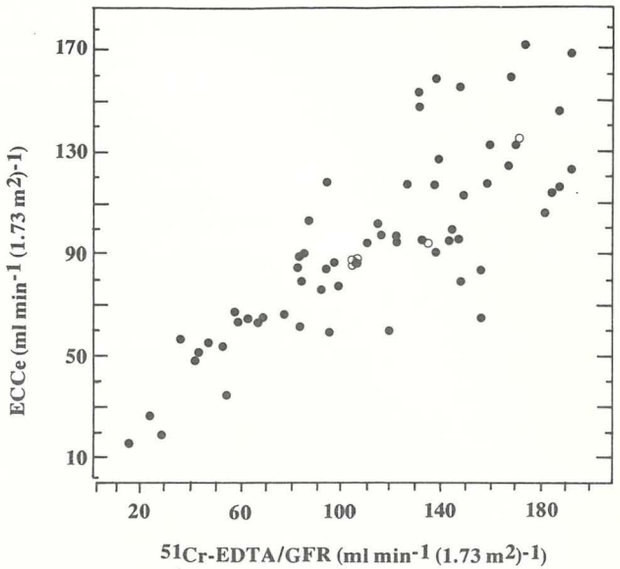

Figure 2 - Comparison of estimated endogenous creatinine clearance (ECCe) (from plasma creatinine) with glomerular filtration rate as measured by ^{51}Cr-EDTA (^{51}Cr-EDTA/GFR) in 30 diabetic patients. Spearman's correlation coefficient (r_s) was 0.82. P<0.05.

Several factors have been blamed for the inaccuracy of ECC measurements. Probably the most relevant is the completeness of 24-h urine collection, especially in outpatients. The precision of ECC can be increased by using mean values of repeated determinations (1) or by employing exactly timed overnight urine collections (11).

A second factor which is particularly important in diabetic patients is the creatinine assay because ketone bodies (12) and glucose (11) may interfere with the method. Serum creatinine may be falsely raised by hyperbilirubinemia or by drugs such as rifampicin (5). Tubular creatinine secretion is increased in the nephrotic syndrome (13) and is reduced by salicylates, cimetidine and trimethoprim (5). Furthermore, there is a decrease in creatinine secretion with age, probably related to a decrease in body mass (7). Therefore, ECC may overestimate the decline of GFR that occurs naturally after the 5th decade. This last factor may have contributed to the discrepancy observed between ^{51}Cr-EDTA/GFR and ECC in our study, because several of the patients described were "more than 50 years old".

The good correlation observed between ECCe and ^{51}Cr-EDTA/GFR may be explained by the fact that the formula of Cockroft and Gault does not depend on urine collections and it takes into account age and weight, which are factors contributing to variability in urinary creatinine excretion.

Based on these findings, we suggest that GFR estimation (in diabetic patients) using ECC must take into account the limitations of the method. Other simpler and less expensive techniques such as ECCe and plasma creatinine should be preferred in routine

practice. In special situations, such as kidney transplantation or in patients with progressive nephropathies (e.g. diabetic nephropathy) (14), ^{51}Cr-EDTA/GFR, a more accurate method, should be used.

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