Letters and Replies

Validity of rapid estimation of glomerular filtration rate in type 2 diabetic patients with normal renal function

Sir,

We would like to comment on the paper ‘Validity of rapid estimation of glomerular filtration rate in type 2 diabetic patients with normal renal function’ by Nielsen et al. [1]. In this study of patients with a GFR >70 ml/min the authors conclude that the Cockcroft–Gault (CG)-formula underestimates $^{51}$Cr-EDTA plasma clearance (GFR) significantly by a mean value of 21%, but up to 40% for higher GFR-values. This is in contrast to our results in a equally large patient-group with type 2 diabetes in various stages of nephropathy (normo-, micro- and macroalbuminuria) and GFR >40 ml/min/1.73m² (plasma creatinine <180 µmol/l) [2]. We suggest that the difference between the two studies is probably caused by the plasma creatinine assay used: a time-reaction method, also called modified Jaffé or alkaline picrate assay. Although it is claimed in the article that this method minimizes interference from non-creatinine chromogens [3], there is still considerable interference compared with the enzymatic and HPLC (reference) assay [4–6]. In a second analysis of our study comparing various plasma creatinine assays, the mean alkaline picrate value for plasma creatinine was 115 µmol/l (SD 28 µmol/l), opposed to 93 and 96 µmol/l (SD 30 and 34 µmol/l respectively) for the enzymatic (creatinase; PAP) and HPLC-assays [7]. Because creatinine is in the denominator of the CG-formula, the use of an alkaline picrate assay will lead to inappropriately low results compared to GFR; this is especially so in the higher GFR range, when plasma creatinine values are lower and overestimation by the alkaline picrate method is larger in terms of percentage. In our study we found an overestimation of GFR by CG using an enzymatic assay, but this overestimation disappeared completely over the whole range of GFR measurements (urinary clearance of continuously infused [125I]iothalamate), when we administered cimetidine 2400 mg orally over 24 h [2]; doing so, we inhibited tubular creatinine secretion and obtained a higher plasma creatinine value next day, which we used to calculate the CG-formula.

The use of an alkaline picrate plasma creatinine assay explains in our opinion the significant underestimation of GFR by the CG-formula’ in the study of Nielsen et al. In the seven other quoted studies in their article, in which GFR-estimation by the CG-formula gave conflicting results, neither an enzymatic plasma creatinine assay nor cimetidine were used, in our opinion necessary for accurate GFR-estimation. We hope that in the future more studies on GFR-estimation will be done using these two refinements for calculation of the CG-formula.

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Reply

Sir,

We recently showed [1] that estimation of GFR using the Cockcroft–Gault formula [2] underestimated the GFR ($^{51}$Cr-EDTA plasma clearance rate) in type 2 diabetic patients with normal renal function (GFR >70 ml/min). We also pointed out the inconsistent literature on this matter with studies showing both over- and under-estimation of the GFR. The Cockcroft–Gault formula was initially derived with the intention of providing a quick and reliable estimate of GFR based upon gender, age, weight and serum creatinine [2], at a time where specific HPLC or enzymatic creatinine assays were not readily available. The creatinine method used by Cockcroft and Gault in their original publication, was ‘... found to give values close to those found by methods which measure non-creatinine chromogens for serum creatinine ...’ [2], a fact that probably affected the size of the constant found in the denominator of their formula. Similarly, we [1] measured plasma creatinine by a time reaction technique (modified Jaffé’s reaction) [3] which is known to overestimate plasma creatinine, as compared with the more specific HPLC or enzymatic assays, due to interference from non-creatinine chromogens. Thus, the underestimation observed in our study cannot be explained by differences in the plasma creatinine methods assay since we used a method similar to the one used by Cockcroft and Gault.

Testing a proposed formula requires methods as identical to those used in the original proposal. Altering the prerequisites of a formula will potentially introduce systematic ‘errors’ of the estimates. However, modifications of prerequisites are warranted when new formulas are derived or old ones are improved. Dr Kemperman used a different method for measurement of creatinine concentrations when testing the Cockcroft–Gault, namely a method which is known to give lower (although more correct) values than the older time reaction method [4,5]. It is therefore not surprising that they found higher estimates of GFR using the Cockcroft–Gault formula in conjunction with an enzymatic assay [4,5], since plasma creatinine appears in the denominator of the formula (as also noted by the authors). In fact
they found that the Cockcroft–Gault formula overestimated isotopically determined GFR in normoalbuminuric type 2 diabetic patients. Therefore, the contributions by Dr Kemperman et al. should not be considered a test of the Cockcroft–Gault formula in type 2 diabetic patients but rather suggests an improvement. We agree that further studies should be encouraged aiming at improving older, or deriving new, formulas or nomograms that better predict isotopically determined GFR in selected patient groups.

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