Improvements in the use of plasma creatine as a marker of the glomerular filtration rate
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Summary and conclusions
Summary

In patients with renal disease or with systemic disease at risk for deterioration of renal function, knowledge of the glomerular filtration rate (GFR) is important to assess the severity of renal involvement or the response to treatment. The reference value for GFR is 90-170 ml/min/1.73m² for males and 90-150 ml/min/1.73m² for females. Most often an approximation of the GFR is obtained from the plasma creatinine concentration, although this parameter is not only dependent on GFR but also on muscle mass. This can be overcome by the use of formulas or nomograms for GFR-estimation, incorporating age, gender and body weight as a measure of muscle mass, such as the formula of Cockcroft and Gault. As plasma creatinine is not only filtered by the glomeruli, but also secreted in a varying degree by the renal tubules, some overestimation of GFR from plasma creatinine is likely to occur. However, the plasma creatinine concentration is higher during administration of certain drugs, due to inhibition of tubular creatinine secretion. This side-effect can be applied to obtain an improvement of GFR-estimation from plasma creatinine, because during complete inhibition the excretion of creatinine is only dependent on glomerular filtration. Another problem is that the determination of the plasma creatinine concentration by the generally used alkaline picrate (or Jaffé) assay is inaccurate. This assay is based on a color reaction and is liable to interference from non-creatinine chromogens, both endogenous substances and certain drugs. This can be overcome by the use of an enzymatic plasma creatinine assay.

In this thesis improvement of plasma creatinine as a marker of GFR has been studied, using the formula of Cockcroft and Gault, inhibition of tubular creatinine secretion by cimetidine and an automated enzymatic plasma creatinine assay. In chapter 1 a survey is given of the literature on GFR-estimation from plasma creatinine, using prediction formulas. Such formulas overestimated GFR in the low range and underestimated GFR in the normal to high range, if inhibition of tubular secretion and an enzymatic assay were omitted. When the usefulness of a formula is assessed both the accuracy and the precision are important. Accuracy, or bias, is the mean difference from the simultaneously determined 'gold standard' in a representative patient group. Precision is represented by the standard deviation of the difference from GFR in this group. The accuracy and precision of GFR-estimation by the Cockcroft-Gault formula were acceptable in patients with mild to moderate renal insufficiency. Newer formulas did not improve GFR-estimation importantly.

GFR-estimation in the clinical studies (chapter 2 to 4) was performed by the endogenous creatinine clearance, based on 24-hour urine collections, and the formula of Cockcroft and Gault,
before and after administration of cimetidine for 24 hours (see abbreviations and formulas). The GFR measured as the urinary or renal clearance of continuously infused $^{125}$I-iothalamate was considered the 'gold standard'. Patients with gross overweight (body mass index $>30$ kg/m$^2$) or edema were excluded, because in these patients muscle mass is overestimated by body weight. As a consequence the Cockcroft-Gault formula, where body weight is in the numerator, will overestimate GFR. Also, plasma creatinine above 180 $\mu$mol/l was an exclusion criterium. This is because plasma creatinine has to attain a new steady state, when tubular secretion is inhibited by cimetidine. The time to reach this new steady state is dependent on the disappearance rate of creatinine from the circulation, which is dependent on renal function. If plasma creatinine is above 180 $\mu$mol/l, a new steady state may not be reached within 24 hours of cimetidine administration. For practical purposes we did not want a longer administration period. The maximum allowed cimetidine dose of 2400 mg daily was used.

In chapter 2 a study is reported of patients with type 2 diabetes mellitus and various stages of albuminuria. In contrast to the statement above, we allowed patients with a BMI of 30-35 kg/m$^2$ in the study, because many type 2 diabetics are in this BMI-range. The accuracy of GFR-estimation improved after cimetidine administration, but the precision did not. The precision of the endogenous creatinine clearance was less good than that of the Cockcroft-Gault formula. There was a slight tendency of the Cockcroft-Gault formula after cimetidine to underestimate GFR in patients without microalbuminuria or overt nephropathy, and to overestimate GFR in patients with a BMI $>30$ kg/m$^2$.

However, while the accuracy of GFR-estimations was good in patients with type 2 diabetes mellitus, the precision was less than in patients with renal disease. We hypothesized that this was due to patient-specific factors, such as the weight-to-muscle mass ratio and that this was to some extent a constant, systematic error. If so, then follow-up of GFR-estimates by the Cockcroft-Gault formula after cimetidine might still give a good reflection of the change in 'gold standard' GFR. In chapter 3 this follow-up study was described. It appeared that the discrepancy between GFR and the Cockcroft-Gault formula was similar after an interval of two years. Therefore, the change in GFR was represented well by the change in Cockcroft-Gault formula, although the changes were rather small.

While GFR-estimation was accurate for patients with type 2 diabetes mellitus, we wanted to know whether this was also true for renal transplant recipients, as in these patients assessment of GFR is also important for clinical management and for analysis of the success of kidney
transplantation. In chapter 4 a study is reported where the endogenous creatinine clearance without cimetidine and the Cockcroft-Gault formula with cimetidine were compared in relation to a 'gold standard' GFR-measurement. The endogenous creatinine clearance was higher than GFR in each patient. The Cockcroft-Gault formula had a far better accuracy and also a better precision for GFR-estimation than the endogenous creatinine clearance. In the low GFR-range, below 40 ml/min/1.73m², a relative overestimation of GFR by the Cockcroft-Gault formula was observed.

The relevance of the plasma creatinine assay was investigated in chapter 5. We compared an alkaline picrate and an enzymatic assay to the reference high performance liquid chromatography (HPLC) method. Plasma creatinine concentrations, when measured with the alkaline picrate assay, were considerably higher than with the other methods. As plasma creatinine is in the denominator of the formula of Cockcroft and Gault, the GFR-estimates from this formula were considerably lower than the 'gold standard' GFR. GFR-estimation was equal to GFR, when the automated enzymatic or more laborious HPLC method was used.

The plasma creatinine assay is especially important in situations where an increased level of endogenous substances interfering with this assay is encountered, such as ketone bodies in ketoacidosis. In patients with diabetic ketoacidosis an alkaline picrate and an enzymatic assay were compared to the reference HPLC-method (chapter 6). At presentation of ketoacidosis, the median alkaline picrate creatinine value was more than 50 % higher than the median enzymatic or HPLC-value. The difference between the latter two was negligible. The positive error of the alkaline picrate assay was correlated to the acetoacetate concentration and therefore, decreased during treatment of ketoacidosis with insulin and fluid resuscitation. β-hydroxybutyrate, another ketone body, did not add to this positive error. Such a considerable overestimation at presentation of this life threatening disorder may cause a wrong judgement of the hydration status and the renal function, leading to inappropriate treatment or diagnostic steps.

The GFR-measurement that served as the 'gold standard' in the clinical studies was described in detail in the appendix. The classic reference method for GFR is the urinary or renal clearance of the GFR tracer inulin during continuous infusion and bladder catheterization as described by Homer Smith. He assumed stable plasma concentrations of the GFR tracer during continuous infusion, but more recent studies in normal individuals and in renal patients have shown that this is in fact not correct due to the circadian rhythm of GFR. Therefore, a correction for changing plasma tracer concentrations is necessary. Furthermore, bladder catheterization is inconvenient
for patients and may cause urinary tract infection. But when omitted, inaccurate urine collections can ensue which in turn lead to inaccurate GFR-measurements from the urinary clearance. As the infusate and urinary clearance during continuous infusion of $^{131}$I-hippuran are equal for measurement of the effective renal plasma flow, a correction can be made for inadequacies in urine collections. When a simultaneous clearance measurement with the GFR tracer $^{125}$I-iothalamate is performed, the corrected urinary clearance of $^{125}$I-iothalamate without bladder catheterization is an accurate and achievable measure of GFR, with a day-to-day variability of 2.2%.

The following conclusions can be drawn from this thesis:

1. Accurate GFR-estimation from plasma creatinine can be obtained, when applied in the formula of Cockcroft and Gault after inhibition of tubular creatinine secretion by administration of cimetidine for 24 hours, in patients with diabetes mellitus type 2 and renal transplant recipients.

2. The precision of GFR-estimation is less in type 2 diabetic than in renal patients, but differences between GFR and the Cockcroft-Gault formula are patient-specific and consistent in time. Therefore, the Cockcroft-Gault formula can be used for follow-up of the GFR in type 2 diabetic and probably also other patients with renal disease.

3. The endogenous creatinine clearance, measured from 24-hour urine collection, is less accurate and precise for estimation of GFR than the Cockcroft-Gault formula. This method of determination of renal function should be abandoned.

4. The use of a plasma creatinine assay, lacking interference from non-creatinine chromogens, is necessary for accurate GFR-estimation.

5. The plasma creatinine assay can have an impact on the clinical judgement of patients with diabetic ketoacidosis, due to a large positive error of the alkaline picrate (or Jaffé) assay, compared to the automated enzymatic or HPLC-methods.