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Review

Estimation of renal function in patients with diabetes

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Abstract

Diabetes is the leading cause of chronic kidney disease (CKD), which makes estimation of renal function crucial. Serum creatinine is not an ideal marker of glomerular filtration rate (GFR), which also depends on digestive absorption, and the production of creatinine in muscle and its tubular secretion. Formulas have been devised to estimate GFR from serum creatinine but, given the wide range of GFR, proteinuria, body mass index and specific influence of glycaemia on GFR, the uncertainty of these estimations is a particular concern for patients with diabetes. The most popular recommended formulas are the simple Cockcroft–Gault equation, which is inaccurate and biased, as it calculates clearance of creatinine in proportion to body weight, and the MDRD equation, which is more accurate, but systematically underestimates normal and high GFR, being established by a statistical analysis of results from renal-insufficient patients. This underestimation explains why the MDRD equation is repeatedly found to give a poor estimation of GFR in patients with recently diagnosed diabetes and is a poor tool for reflecting GFR decline when started from normal, as well as the source of unexpected results when applied to epidemiological studies with a 60 mL/min/1.73 m^2 threshold as the definition of CKD. The more recent creatinine-based formula, the Mayo Clinic Quadratic (MCQ) equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) improve such underestimation, as both were derived from populations that included subjects with normal renal function. Determination of cystatin C is also promising, but needs standardisation.
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Keywords: Creatinine; Cystatin C; Glomerular filtration rate; Chronic kidney disease; Metformin; Diabetes; Review

Résumé

Estimation de la fonction rénale chez les patients diabétiques.

Le diabète est une cause majeure d'atteinte rénale, estimer la fonction rénale des patients diabétiques est donc crucial. La créatininémie n'est pas un marqueur idéal du débit de filtration glomérulaire (DFG), car elle dépend aussi de l'absorption digestive et de la production musculaire de créatinine, ainsi que de sa sécrétion tubulaire. Des équations intégrant des données anthropométriques doivent donc être utilisées pour estimer le DFG, avec des incertitudes particulières pour les patients diabétiques du fait du large éventail de DFG, de protéinurie, d'index de masse corporelle, et de l'effet propre de la glycémie. Les plus utilisées et recommandées sont la formule de Cockcroft–Gault, simple mais peu précise et biaisée car elle estime la clairance de la créatinine comme proportionnelle au poids, et l'équation de la MDRD, plus précise mais qui sous-estime les DFG normaux car elle a été établie à partir d'une population d'insuffisants rénaux. Cette sous-estimation explique ses mauvaises performances pour estimer le DFG dans des groupes de patients diabétiques récents pour estimer le déclin du DFG en partant de valeurs normales, et aussi certains résultats inattendus d'études épidémiologiques ayant utilisé le seuil de 60 mL/min/1,73 m^2 pour définir l'atteinte rénale. La sous-estimation est moindre avec les équations plus récentes (Mayo Clinic Quadratic, CKD-EPI) qui ont été établies à partir de populations incluant des sujets sans insuffisance rénale. La cystatine C est aussi un progrès pour l'estimation du DFG mais nécessite une standardisation.
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Mots clés : Créatininémie ; Cystatine C ; Débit de filtration glomérulaire ; Atteinte rénale ; Metformine ; Diabète ; Revue

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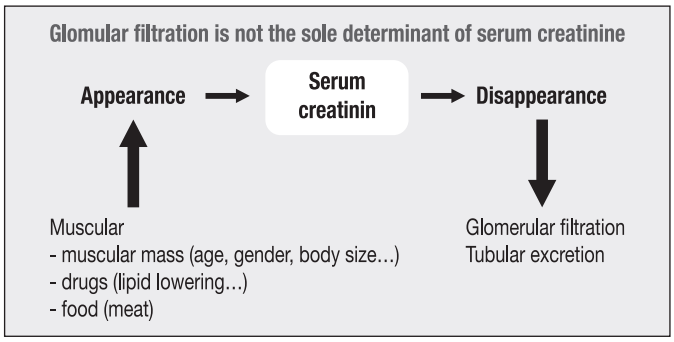

Fig. 1. Serum creatinine does not solely depend on glomerular filtration rate (GFR).

1. Introduction

Diabetic nephropathy affects around one-third of patients with diabetes [1], and is the primary cause of end-stage renal disease in most countries [2]. According to the recommendations of the American Diabetes Association and National Kidney Foundation, the critical parameters for the detection [3] and follow-up [4] of chronic kidney disease (CKD) in patients with diabetes are the albumin excretion rate (AER) and glomerular filtration rate (GFR), which is poorly assessed by the sole determination of serum creatinine, as estimated (e-GFR) by either the Cockcroft–Gault (CG) or the Modification of Diet in Renal Disease (MDRD) equation. An increased AER reflects damage to the glomerular filtration barrier—specifically, endothelial cells, glomerular membrane and podocytes. A reduced GFR reflects impaired renal function. An e-GFR less or equal to 60 mL/min/1.73 m^2 and/or an AER greater than 30 mg/24 h suggest the diagnosis of CKD.

2. Serum creatinine is not an ideal marker of glomerular filtration rate

Serum creatinine does not depend solely on GFR (Fig. 1). Besides the exogenous source of ingested meat, creatinine is mainly produced from muscles and depends on muscle mass, which is higher in males and in black people, and lower with age in adults. This means that adjusting serum creatinine values for ethnic and anthropometric parameters, as performed by formulas, improves their relationship to GFR. The influence of muscle mass on serum creatinine is illustrated by the 20–30 μmol/L creatininemia usually found in patients with Duchenne myopathy [5]. However, whether more subtle reductions of muscle mass as seen, for example, in sedentary people can affect serum creatinine is not known. Less dramatically, drugs such as fibrates can affect the muscle production of creatinine [6] and alter the reliability of GFR estimations in patients with diabetes [7]; this effect, however, does not explain the increased creatinine observed in the Helsinki Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, as cystatin C (CysC) was also increased in the patients treated with fenofibrate during the trial [8]. On the other hand, clearance of creatinine from plasma does not only rely on GFR, but also on its tubular secretion: creatinine clearance exceeds GFR by +10% in normal healthy subjects. This difference can increase to +60% in highly proteinuric nephropathies such as the nephrotic syndrome, with apparently normal serum creatinine masking frank alterations of GFR [9].

3. Serum creatinine is especially imperfect in patients with diabetes

A broad range of GFR can be encountered in diabetic patients, ranging from normal if they are not affected by diabetic nephropathy to high at the early 'hyperfiltration stage' [10] and to very low at the terminal predialysis stage. Proteinuria shifts from normal to the nephrotic range in the presence of CKD [11,12]. The consumption of red meat is higher in men with type 2 diabetes [13], and may become worse with the vogue for high-protein diets. The muscle mass of patients with diabetes is especially altered with age [14], and even more so in the case of renal insufficiency [15], while body weight varies according to the type of diabetes, which can influence the estimation of GFR. Variations in glycaemia can also directly influence GFR, as demonstrated in both normal subjects [16] and in those with type 1 (T1D) and type 2 diabetes (T2D) [17,18]. The importance of the glucose level was illustrated by the work of Remuzzi et al. [19], who measured GFR under conditions of controlled glycaemia in patients with T1D complicated by nephropathy: 35 mL/min/1.73 m^2 with a plasma glucose of 3.3 g/L vs 21 mL/min/1.73 m^2 with a plasma glucose of 0.93 g/L. These numerous influences make the estimation of GFR mandatory, but they also raise concerns over the validity of the formulas used in such a patient population.

4. The conventional formulas: Cockcroft–Gault or modification of diet in renal disease?

The recommended equations are the old Cockcroft–Gault formula, where CG = [(140 − age in years) × body weight in kg × K] divided by serum creatinine in μmol/L, and K is a constant: 1.23 for men and 1.04 for women [20], and the MDRD study equation [21], where MDRD = 175 × (serum creatinine in mg/dL)$^{-1.154}$ × (years)$^{-0.203}$ × (0.742 if female) × (1.210 if African-American). The results of the MDRD are directly expressed adjusted to body surface area, whereas the results of the CG have to be adjusted, usually using the DuBois formula [22]. It should be noted that this correction is not always done in clinical practice. On comparing the results of both estimations to GFR measured by an isotope reference method (^{51}Cr-EDTA) in 160 patients with both types of diabetes (n = 50 T1D, n = 110 T2D) and a wide range of renal function (serum creatinine 54–371 μmol/L, isotopic GFR 60.9 ± 36.3 mL/min/1.73 m^2) [23], the MDRD was better correlated to GFR (r = 0.81) than was the CG (r = 0.74). Also, the receiver operating characteristic (ROC) curve analysis demonstrated greater diagnostic accuracy for the MDRD (Fig. 2). These results are in line with those of Froissard et al. [24], who also found the greater precision of the MDRD to be more effective in non-diabetic subjects (n = 2095), and of Poggio et al. [25], who found that, in 246 patients with diabetes and renal

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