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Editorial Comment

EDITORIAL COMMENT

Muscle mass, creatinine, cystatin C and selective glomerular hypofiltration syndromes

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ABSTRACT

In this issue of *Clinical Kidney Journal*, Stehlé and colleagues demonstrate that estimation of glomerular filtration rate (GFR) by use of creatinine and a measure, total lumbar muscle cross-sectional area, reflecting the total muscle mass of an individual, is superior to GFR-estimating equations based upon creatinine and demographic variables. The report by Stehlé *et al*. demonstrates one solution to the interference of muscle mass in the use of creatinine to estimate GFR. This interference was identified already at the start, in 1959, of using creatinine for estimation of GFR. Different ways of taking the muscle mass into account when creatinine-based estimations of GFR have been used generally include use of controversial race and sex coefficients. A new marker of GFR, cystatin C, introduced in 1979, has been shown to be virtually uninfluenced by muscle mass. In this editorial, the simultaneous use of creatinine and cystatin C to estimate GFR, muscle mass and selective glomerular hypofiltration syndromes is described.

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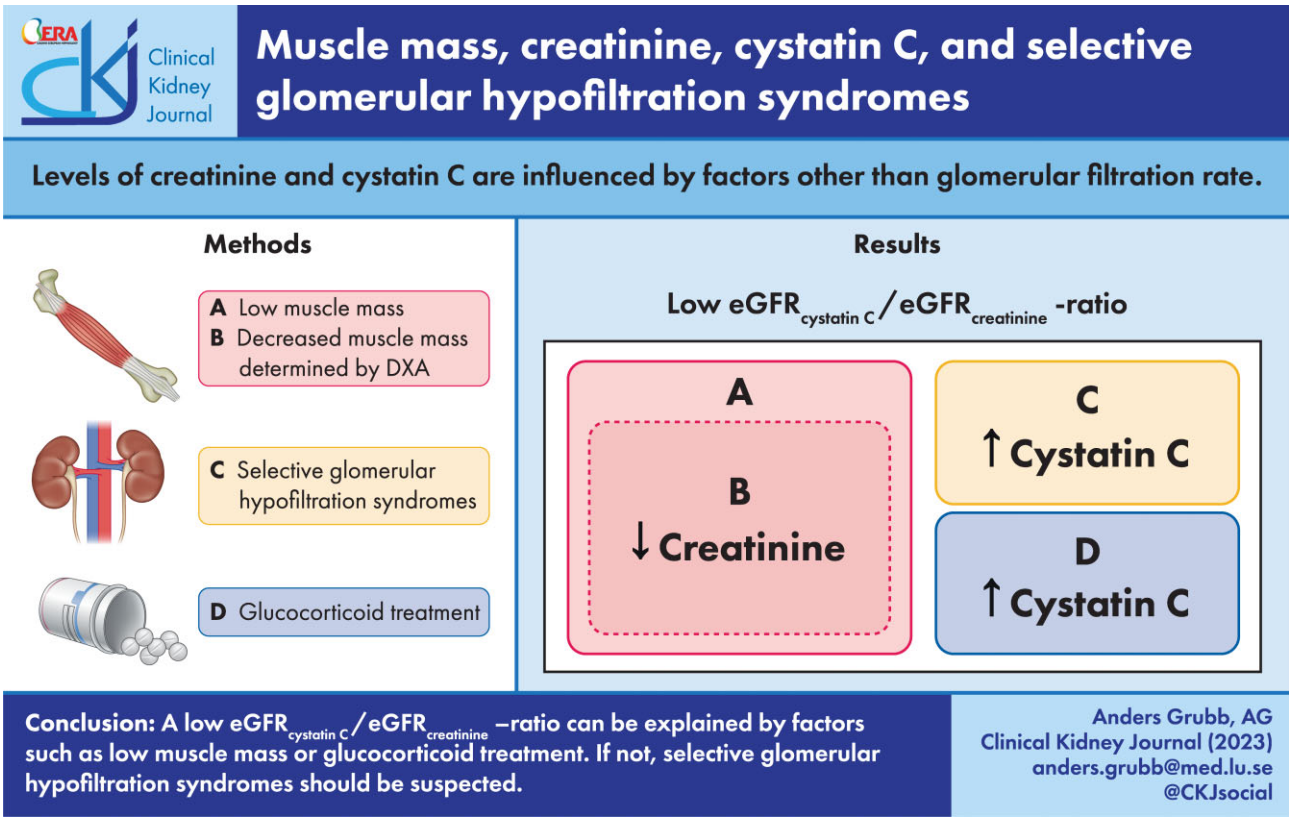
GRAPHICAL ABSTRACT



Keywords: creatinine, cystatin C, sarcopenia, selective glomerular hypofiltration, shrunken pore syndrome

CREATININE, MUSCLE MASS, SEX AND RACE COEFFICIENTS

The introduction of endogenous creatinine clearance as a measure of glomerular filtration rate (GFR) by Rehberg in 1926 [1] developed in 1959 and 1971 into using plasma or serum creatinine for estimation of GFR [2, 3] and, later, to the use of more complex creatinine-based GFR-estimating equations [4]. However, even the first reports suggesting serum creatinine as a potential marker of GFR observed that increasing muscle mass produced increasing serum levels of creatinine and that a sex coefficient had to be used to estimate GFR in males and females due to the fact that the average muscle mass in males is 10%–25% bigger than in females [2, 3]. Indeed, some investigations also show that for healthy people with normal measured GFR (iohexol clearance), the creatinine level is significantly correlated to the measured muscle mass (dual-energy X-ray absorptiometry, DEXA) of the individuals, but not to their GFR [5]. It was also noted that different populations display different average muscle mass and in 1999 the first creatinine-based GFR estimating equation using race coefficients was described [6]. Since then, at least 10 different race coefficients have been used in creatinine-based GFR-estimating equations [7]. This has been an unfortunate development as 'race' cannot be determined by biological measurements [8–11], and usually is based upon self-reporting [12]. The concept of race is therefore subjective and more associated with sociological circumstances than objective biological facts [12]. It is also associated with discomfort of the self-reporting individual, and misclassification may lead to reduced access to care [12]. Therefore, strong recommendations have recently been issued that race coefficients should not be used in creatinine-based GFR-estimating equations [7, 13–15], and a new creatinine-based GFR-estimating equation without a race coefficient has recently been described [16]. As expected, its diagnostic performance was reduced compared with the corresponding equation with a race coefficient [16]. Another way of avoiding race coefficients in creatinine-based GFR-estimating equations is to measure total lumbar muscle cross-sectional area by unenhanced CT scan at the third lumbar vertebra and include this value in the GFR-estimating equation, as described by Stehlé *et al.* in this issue of *Clinical Kidney Journal* [17].

Although use of race coefficients in creatinine-based equations is problematic and should be avoided, the use of sex coefficients might also be problematic [7]. Although it for many years has been assumed that the sex of a person always is a binary parameter, recent research has demonstrated that this is not the optimal description of reality [18–20]. The construction of creatinine-based GFR-estimating equations has previously always assumed that sex is a binary parameter, but today several nations, e.g. Germany, the USA, Australia, Canada, India, Sweden and Denmark, have applied recent research and specify more than two genders in basic descriptions of their citizens [21]. Self-reporting of sex is often used in healthcare and if only two alternatives are allowed, a significant proportion

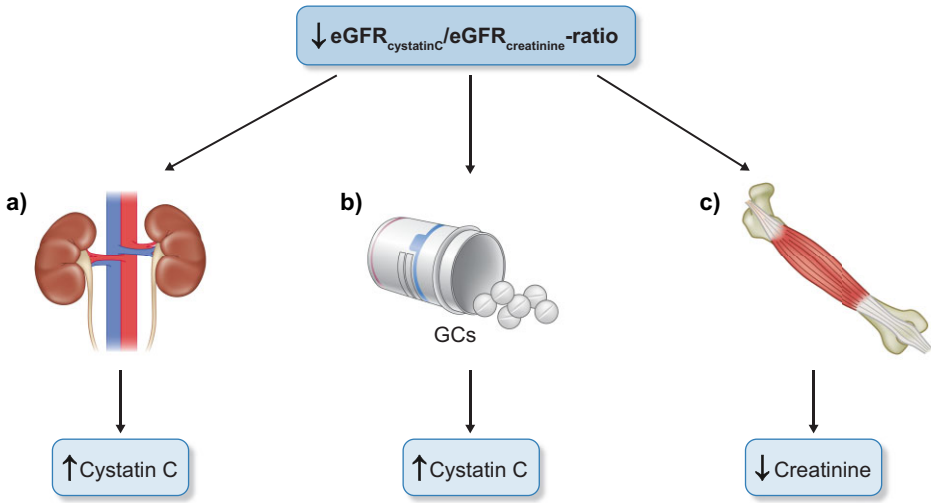


Figure 1: A low eGFRcystatin C/eGFRcreatinine ratio usually indicates a) selective glomerular hypofiltration disorders e.g., shrunken pore or elongated pore syndromes, b) glucocorticoid treatment or c) sarcopenia.

of the patients will experience discomfort connected to the acknowledgment of only two genders in national legislations and other issues pertaining to the LGBTQIA+ spectrum [22, 23]. An additional problem connected to self-reporting of sex is that a change in the self-reported sex results in a major change in creatinine-based estimations of GFR [24]. These problems associated with the use of sex coefficients will be eliminated by use of the GFR-estimating equation described by Stehlé *et al.* in this issue of *Clinical Kidney Journal* [17]. However, there may be an easier way to avoid confounding from muscle mass.

CYSTATIN C, MUSCLE MASS, SEX AND RACE COEFFICIENTS

Already in the initial studies of the relationship between GFR and cystatin C, it was shown that no sex coefficient was required to obtain a high correlation between GFR and cystatin C [25], in contrast to when creatinine was used [25]. This suggested that differences in muscle mass between individuals did not interfere in cystatin C–based estimation of GFR, meaning that no sex or race coefficients would be required in cystatin C–based GFR-estimating equations. Indeed, several recent studies of cystatin C and GFR have demonstrated that neither race nor sex coefficients are required in cystatin C–based GFR-estimating equations [7, 26–29]. Therefore, use of cystatin C–based GFR-estimating equations is an easy option for avoiding the use of race or sex coefficients in estimation of GFR.

ANALYSING MUSCLE MASS AND SARCOPENIA

Even if the measurement of muscle mass and using this parameter in creatinine-based GFR-estimating equations, as described by Stehlé *et al.* in this issue of *Clinical Kidney Journal*, allows omission of race and sex variables in such equations [17], reliable measurement of muscle mass is technically difficult and time consuming [5, 17]. The diagnosis of sarcopenia, a state of both low muscle mass and low strength, requires the measurement of appendicular skeletal muscle mass, for example using DEXA and grip strength to estimate muscle strength [30]. Since creatinine, in contrast to cystatin C, is strongly related to the muscle mass of a person and both analytes are related to GFR, easier and less expensive ways have been suggested to estimate the muscle mass status of a person. One example of this is the Sarcopenia Index [(serum creatinine/cystatin C) × 100], recently suggested to be useful for monitoring musculoskeletal status in drug trials aiming to treat sarcopenia [31]. Ratios between cystatin C– and creatinine-based GFR estimates have also been used to estimate muscle mass and a $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio below about 0.90 has in many studies been found to indicate a low muscle mass [5, 32–41].

Identifying individuals suffering from sarcopenia is important, since it is a key component of frailty, a state of functional decline in multiple organ systems [41, 42].

IDENTIFYING SELECTIVE GLOMERULAR HYPOFILTRATION SYNDROMES

Although a low $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio usually indicates a low muscle mass, it might also identify another group of syndromes called selective glomerular hypofiltration syndromes first described in 2015 [43–48]. In these syndromes, e.g. shrunken and elongated pore syndromes, the glomerular filtration of 5–30 kDa molecules, such as cystatin C, is selectively reduced compared with the filtration of small molecules <1 kDa dominating the glomerular filtrate, e.g. water, creatinine and urea [44, 45]. Although the changes in the curves relating sieving coefficients to molecular mass of the filtered molecules in these syndromes usually are obvious from the changes in the resulting proteomes, a few invasive studies showing the same phenomena have also been performed, especially in pregnancy [49]. In the third trimester of all pregnancies the filtration of 5–30 kDa molecules is selectively reduced, but a few weeks after birth the filtration curves are normalized [44, 45]. Selective glomerular hypofiltration syndromes display a prevalence between 0.3% and 36% in different populations [44, 45] and are strongly connected to increases in mortality or morbidity [44–48]. The pathophysiological mechanism explaining the increase in mortality and morbidity in these conditions is probably connected to the altered proteomes [44, 45]. Whether a decreased $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio indicates sarcopenia or selective

glomerular hypofiltration syndromes is often obvious from clinical observations on muscle weakness, low body mass index and progressive muscle wasting, but in some cases measuring muscle mass might be required, e.g. as described by Stehlé *et al*. [17].

DIAGNOSTIC ALTERNATIVES OF A LOW $eGFR_{cystatin\ C}/eGFR_{creatinine}$ RATIO

The two diagnostic interpretations of a low $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio given above, i.e. sarcopenia and selective glomerular hypofiltration syndromes, must be complemented by the knowledge that treatment of patients with moderate to high doses of corticosteroids will induce an increase in the production of cystatin C, thereby producing a low $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio unrelated to the diagnoses mentioned above [44, 45, 50]. However, in clinical practice the differentiation between these diagnostic alternatives will most often be simple and only rarely require measurement of muscle mass, e.g. as suggested by Stehlé *et al*. in this issue of *Clinical Kidney Journal* [17]. Figure 1 shows the dominating conditions indicated by a low $eGFR_{cystatin\ C}/eGFR_{creatinine}$ ratio.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Stehlé et al. Development and validation of a new equation based on plasma creatinine and muscle mass assessed by CT scan to estimate glomerular filtration rate: a cross-sectional study. *Clin Kidney J* (2023) 16: 1265–1277.)

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