Title

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Journal

Obesity, 27(12)

ISSN

1930-7381

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Publication Date

2019-12-01

DOI

10.1002/oby.22668

Obesity

The Enlarging Effect of Obesity on Estimating Kidney Function: Blaming Serum Creatinine Versus Indexation and Methodology

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Kidney function is usually measured or estimated in the form of glomerular filtration rate (GFR). GFR is commonly expressed as milliliters per minute per 1.73 square meters of body surface area (mL/min/1.73 m^2 BSA). The latter metric, which is often used when the estimated GFR (eGFR) is presented, signifies adjustment of the individual kidney function to a standard BSA to allow commensurate comparison of kidney function across individuals with different body sizes. This approach may lead to erroneously skewed values in persons with morbid obesity, in whom the BSA-indexed eGFR can be misleading relative to the underlying raw GFR values as a result of distortion by a rather large BSA in the denominator. In a landmark study by Guebre-Egziabher et al. (1) in this issue of *Obesity*, the GFR was laboriously measured (mGFR) by either inulin or iohexol, as the gold standards, in 706 adults with morbid obesity and BMI > 35 kg/m^2. The investigators found that the eGFR, using the commonly employed Chronic Kidney Disease-Epidemiology (CDK-EPI) Collaboration and Modification of Diet in Renal Disease (MDRD) equations, overestimated the mGFR that was indexed for BSA; the median values were 56 (CKD-EPI equation eGFR) and 55 (MDRD equation eGFR) versus 50 mL/min/1.73 m^2 BSA (mGFR). After deindexing the GFR data, the median values of eGFR versus mGFR were 67 versus 61 mL/min/1.73 m^2, respectively. The authors concluded that the BSA-indexed eGFR, regardless of the use of CKD-EPI or MDRD equations, tends to overestimate kidney function in morbid obesity. Deindexation did not remedy the biases and inaccuracies of eGFR and indeed worsened the overestimation according to the authors (1).

Whereas serum creatinine is invariably used as the kidney filtration marker, it is derived from muscle-based creatine and thus can serve as a biomarker of skeletal muscle mass in human individuals if appropriate adjustment for kidney function and dietary meat intake is undertaken (2). Higher muscle mass is associated with more favorable clinical outcomes and longevity, including in patients with chronic disease states (2). A dramatic weight loss of 10 to 20 lb in patients who received bardoxolone versus placebo was suggested as the explanation for an observed drop in eGFR in a randomized clinical trial (2,3). In another study, weight loss in diabetes patients reduced serum creatinine from 2.0 to 1.5 mg/dL, and the eGFR increased by 13 mL/min (4). In another study on obesity, an 8% weight loss increased the eGFR by 8.9 mL/min by means of reducing serum creatinine (5). Similarly, fasting for Ramadhan increased the eGFR likely because of loss of muscle and/or reduction of dietary meat intake (6). Notwithstanding these data, it is not clear why the eGFR overestimated the mGFR in morbid obesity in the study by Guebre-Egziabher et al. (1). However, the removal of indexation for BSA did not improve the estimate but worsened it. It is possible that serum creatinine is somewhat lower in patients with morbid obesity as a result of less creatinine generation in the muscle or higher tubular creatinine secretion. Indeed, in a study by Sinkeler et al. (7), a higher BMI was an independent determinant of higher fractional excretion of creatinine, suggesting that higher BMI enhances tubular creatinine handling.

Given the inherent limitation of serum creatinine and the issues related to estimating the GFR based on serum creatinine (whether via MDRD or CKD-EPI) (8), other kidney filtration markers, such as serum cystatin C, are of great interest here (Table 1). Indeed, the same group of investigators (9) recently examined 166 patients with obesity and CKD stages 1 to 5, comparing CKD-EPI equations that use cystatin C, creatinine, or their combination, and found that using cystatin C alone or in combination with creatinine was less biased, especially when eGFR was deindexed. Therefore, it can be argued that the use of serum creatinine in any eGFR formula tends to overestimate the GFR in obesity and that serum cystatin C concentration measurement should be added as a more reliable filtration marker. Thus, by simultaneously measuring serum creatinine and another kidney filtration marker such as cystatin C, along with a biomarker of dietary meat intake to tease out the portion of serum creatinine that may be from higher intake of meat ingestion, we should be able to develop equations that can more reliably estimate kidney function in disease and health, and in particular in persons with morbid obesity and an exceptionally large BSA.O

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See accompanying article, pg. 2011.

Funding agencies: This work was supported by research grants from the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases grant K24-DK091419 to KKZ.

Disclosure: The authors declared no conflict of interest.

Received: 27 August 2019; **Accepted:** 24 September 2019; **Published online 5 November 2019. doi:10.1002/oby.22668**

TABLE 1 Comparing serum cystatin C and creatinine as kidney filtration markers

	Creatinine	Cystatin C
Origin and structure	Derived from creatine in the muscle, with a similar structure as amino acids including nitrogen	Made by all nucleated cells, larger than creatinine
Molecular weight	113 g	13,359 g (13.4 kD)
Muscle mass effect	Larger muscle mass associated with higher levels of creatinine	Similar blood concentrations across different muscle mass
Dietary intake effect	Meat intake may affect creatinine level	Diet has minimal effect on cystatin C
Kidney filtration	Glomerularly filtered and tubularly secreted	Only filtered, no tubular secretion
Impact of demographic factors	Affected by age, gender, and race	Not affected by race
Obesity	May under- and overestimate GFR in obesity	Less confounding in obesity
Inflammation	No direct effect unless inflammation leads to muscle wasting or acute kidney injury	Chronic inflammation may increase cystatin C levels, but often slightly and transiently
Clinical outcomes	Associated with mortality, which may be confounded by muscle mass or meat intake	More linear association with mortality compared with serum creatinine
Disease state	In malnutrition or sarcopenia, serum levels are often lower than expected	May be increased in some malignancies
Other factors	Medications such as cimetidine may affect its tubular secretion	Thyroid supplement therapy and steroids may transiently affect the circulating level
Costs	Usually inexpensive (measurement is included in the basic metabolic panel)	May be slightly more expensive than measuring serum creatinine

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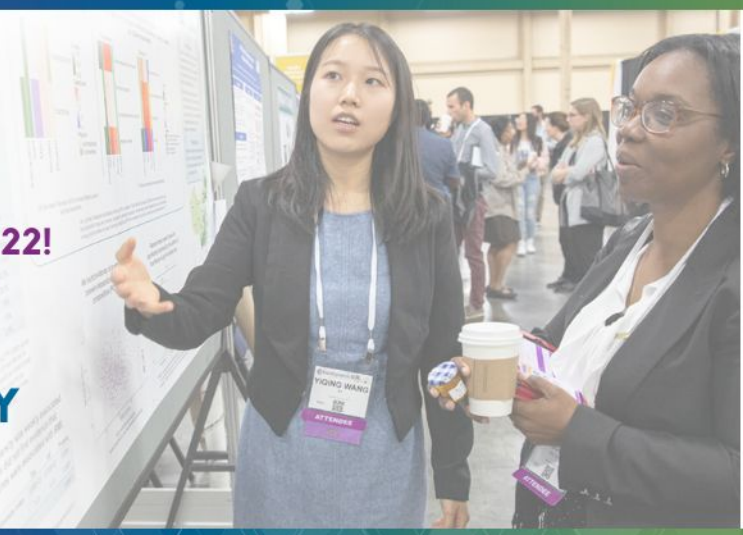

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