Comment on "Higher Serum Creatinine Concentrations in Black Patients with Chronic Kidney Disease: Beyond Nutritional Status and Body Composition"

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The article "Higher Serum Creatinine Concentrations in Black Patients with Chronic Kidney Disease: Beyond Nutritional Status and Body Composition" by Hsu *et al.* (1) suggests that a greater creatinine generation rate on the basis of larger muscle mass does not explain the higher serum creatinine levels observed in black prevalent hemodialysis patients. In our opinion, this conclusion is not tenable given the limitations of the study design and method.

The most critical methodologic shortcoming of Hsu's approach is the choice of 50-kHz single-frequency bioimpedance analysis (BIA) and the way it was used to correct for, as the authors stated, "body composition." Creatinine is predominantly derived from skeletal muscle creatine (endogenous) and, to a lesser extent, from the diet (exogenous); therefore, when attempting to correct for creatinine generation rate by adjusting for body composition, the appropriate body compartment to adjust for is skeletal muscle. 50-kHz single-frequency BIA is not a valid method for delineating body fluid compartments in individuals with altered hydration (2); however, accurate delineation of intracellular volume is essential for estimation of muscle mass by BIA, although even the most accurate BIA-derived measure of intracellular volume will never be a perfect reflection of muscle volume, because BIA cannot distinguish between intracellular water from muscle cells and intracellular water from other tissues, such as the viscera, skin, and adipose tissue. Notwithstanding this, BIA can be a valid tool for estimation of body composition, including in patients with chronic kidney disease (3), and population-specific bioimpedance-based regression models can provide valid muscle mass estimates (4). Of note, though, in individuals with an altered intracellular-to-extracellular volume ratio (*e.g.*, patients with chronic kidney disease), the 0/∞-kHz parallel Cole-Cole model is the method of choice for determining body water compartmentalization, as has been comprehensively shown by Gudivaka *et al.* (2). An adjustment for whole-body resistance and reactance measured at 50 kHz as used by Hsu *et al.*, however, is an oversimplification and an inadequate adjustment for muscle mass. Such an inadequate adjustment would not be expected to eliminate racial differences in serum creatinine even if differences in muscle mass were the only underlying mechanism.

The accuracy of a BIA method for muscle mass estimation should be evaluated against an accepted reference method (with magnetic resonance imaging [MRI] and computed tomography being the best currently available methods for *in vivo* estimation of skeletal muscle volume) (4,5). We have determined whole-body muscle volumes in 27 adult maintenance hemodialysis patients by means of whole-body MRI and compared these, in the same patients, with whole-body resistance and reactance measured at 50 kHz, the technique used by Hsu *et al.*. The bioimpedance measurements were performed on the same day as the MRI scans, and both were performed on a regularly scheduled hemodialysis day before initiation of the dialysis procedure. MRI acquisition was done using a 1.5 Tesla scanner (6X Horizon; General Electric, Milwaukee, WI) and typically involved approximately 40 axial images of 10 mm thickness at 40-mm intervals across the whole body. BIA was performed on the non–vascular access side of the body using a Xitron 4200 device (Xitron Technologies, San Diego, CA). This is a multifrequency (*i.e.*, spectroscopy) device, and the 50-kHz single-frequency readings discussed here were extracted from the raw data files. A detailed presentation of all methods mentioned here can be found in the study by Zhu *et al.* (6). Figure 1 shows the correlation between muscle volume determined by MRI and resistance at 50 kHz ($R^2 = 0.51$). This degree of correlation would not be expected to eliminate muscle-related differences in serum creatinine with adjustment for resistance. Reactance at 50 kHz (Figure 2) practically does not correlate at all with muscle volume measured by MRI ($R^2 = 0.004$). Although this lack of bivariate correlation does not necessarily mean that reactance measured at 50 kHz does not add to the prediction quality of a multiple regression model for estimation of muscle volume, one major flaw remains: Such a model based on single-frequency resistance and reactance still cannot accurately delineate intracellular from extracellular fluid volume. The more uniform the population in terms of hydration status and the more the tested cohort resembles the original individuals with whom the model was developed, the less of a problem this may be, but in individuals with highly varying degrees of fluid status disturbances (*e.g.*, the hemodialysis population), this leads to marked inaccuracies. It is with the use of the 0/∞-kHz parallel Cole-Cole model that the most accurate delineation between intra- and extracellular fluid compartments is accomplished.

That aside, even with a precise adjustment for muscle mass, the study design used by Hsu *et al.* would still have precluded

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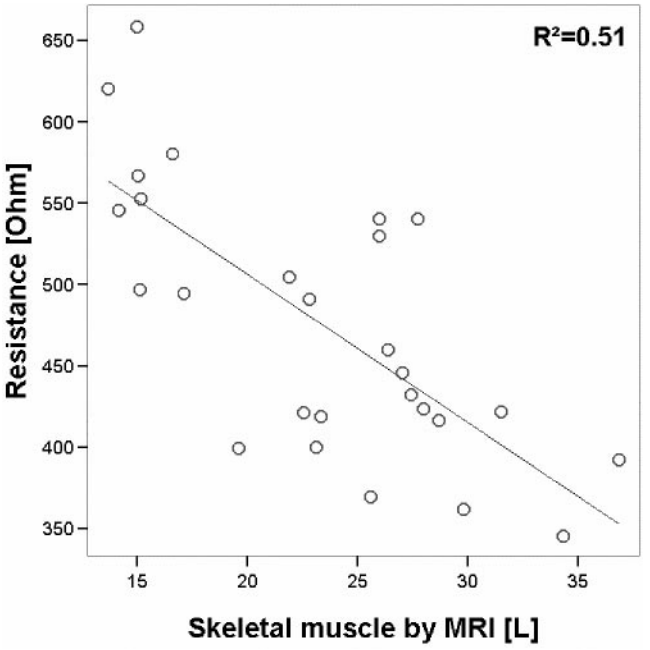

Figure 1. Whole-body resistance measured at 50 kHz with bioelectrical impedance analysis (BIA) in 27 maintenance hemodialysis patients, plotted against whole-body skeletal muscle volume determined by magnetic resonance imaging (MRI). In each individual, BIA and MRI were performed on the same day.

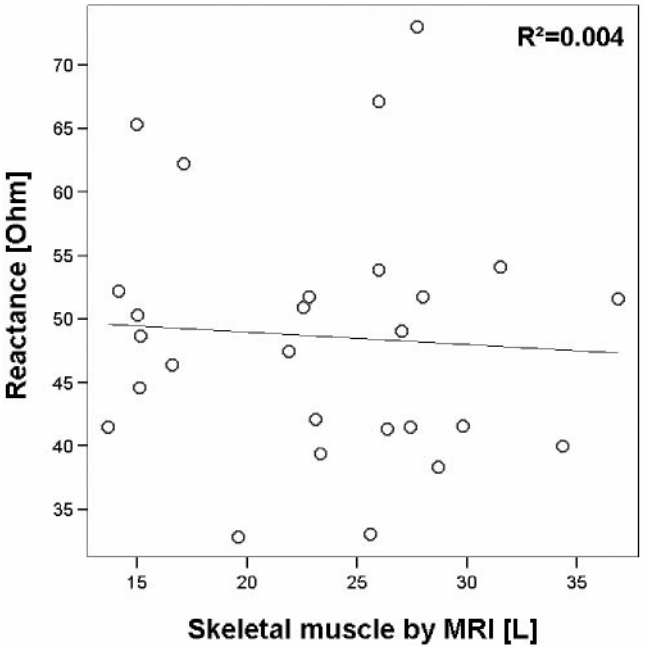

Figure 2. Whole-body reactance measured at 50 kHz with BIA in 27 maintenance hemodialysis patients, plotted against whole-body skeletal muscle volume determined by MRI. In each individual, BIA and MRI were performed on the same day.

the implication that muscle mass does not explain higher serum creatinine levels in black individuals: Predialysis laboratory values, including serum creatinine, were averaged during a period of 3 consecutive months before the BIA. One quarter of 1 yr is enough time for body composition to change significantly. He *et al.* (7) demonstrated that total body potassium, which has been used as an index of muscle mass in several studies (8–12), declines over time and that it does so more rapidly in black than in white individuals. It is conceivable that such different kinetics in body cell loss could lead to a bias toward higher serum creatinine levels in black individuals despite accurate adjustment for muscle mass (Figure 3). When serum creatinine is being related to muscle mass, both parameters, therefore, should be determined at the same time (or at least, if multiple serum creatinine values per individual are averaged, the time period from which these laboratory values stem should be centered around the time of BIA measurement).

Another question that necessarily arises is how well predialysis serum creatinine levels represent muscle mass. On the basis of current understanding of creatinine metabolism, serum creatinine would certainly be expected to correlate with muscle mass, but it is not the only determining factor. Creatinine distribution volume will directly affect predialysis serum creatinine concentration in hemodialysis patients. This is a point that Hsu *et al.* did not address in their discussion. For example, in two anuric hemodialysis patients with identical muscle masses (and, hence, identical creatinine generation rates) and identical creatinine elimination rates but different sizes of creatinine distribution volume, interdialytic rise in serum creatinine will be steeper and reach a higher predialysis concentration in the person with the smaller distribution volume when both receive the same Kt/V_{urea} (Figure 4); therefore, higher predialysis serum creatinine levels are not necessarily a reflection of greater muscle mass in hemodialysis patients.

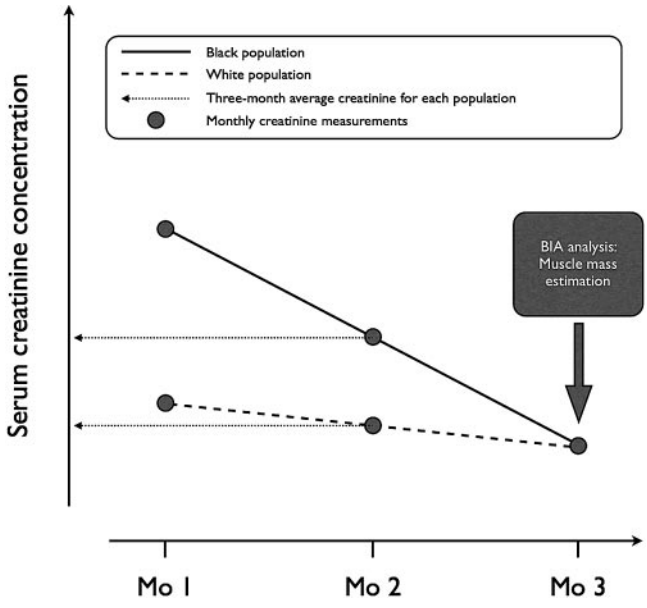

Figure 3. Illustration of how averaging the serum creatinine during a 3-mo period before BIA may create a systematic bias toward higher creatinine levels in black compared with white individuals as a result of different rates of muscle mass loss between those populations. The bias would obviously persist despite adjustment for muscle mass.

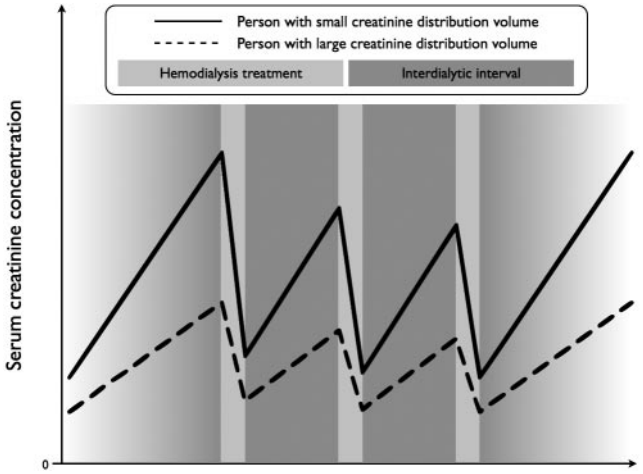

Figure 4. Illustration of how a relatively smaller creatinine distribution volume, at the same rates of creatinine generation and extrarenal creatinine elimination, will result in a steeper interdialytic rise and higher predialysis concentrations of serum creatinine. The figure shows (from left to right) a start-, mid-, and end-week dialysis treatment. For illustrative purposes, the distribution volumes in this simulation differ by a factor of 2, and the intervals (intra-/interdialytic) are not depicted proportionally. The schematic's emphasis is on the pre- and postdialysis serum concentrations; kinetics between these time points are not portrayed accurately. Simulation assumes steady-state conditions; that both individuals receive the same Kt/V_{urea}; and that this is achieved by adjustment of t, not K.

In their discussion, Hsu *et al.* cited a study by Agamah *et al.* (13), who found that racial differences in serum creatinine levels disappeared after adjustment for anthropometric surrogates of body composition, and they stated that a likely reason for the conflicting results between the study by Agamah *et al.* and their own study may be the poor accuracy of anthropometry in assessing body composition. This logic is questionable. Generally, the effect of adjusting for a poorer surrogate of body composition is exactly the opposite. One would expect the racial differences in serum creatinine to *decrease* when *more accurately* accounting for muscle mass.

In regard to the reporting of the results in the article by Hsu *et al.*, it would have been useful to see the adjusted coefficients of multiple determination for their regression models, so as to assess how much of the variation in serum creatinine is accounted for by the included independent variables.

In summary, (*1*) the implication that statistical adjustment for resistance and reactance measured by 50-kHz BIA represents an accurate adjustment for muscle mass is not correct. Failure of adjustment for those parameters to eliminate racial differences in serum creatinine, therefore, is not surprising. (*2*) Averaging of serum creatinine during 3 mo before the BIA measurement may have introduced a systematic bias toward higher creatinine levels in black individuals independent of muscle mass. (*3*) Even in the absence of such bias, the assumption that predialysis serum creatinine levels would even have to be identical in individuals with the same muscle mass is a misapprehension. The authors' statement that differences in body composition do not explain racial differences in serum creatinine levels is not supported by the evidence provided.

Disclosures

None.

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