ARIC Manuscript Proposal #3765

PC Reviewed: 1/12/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Estimated creatinine generation as a measure of muscle mass

b. Abbreviated Title (Length 26 characters): **eGcr as measure of muscle**

2. Writing Group:

Writing group members: Shoshana H Ballew, Morgan Grams, Chris Pierce, Liz Selvin, Dan Wang, Josef Coresh, Lesley A Inker, Andrew S Levey, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SHB__ **[please confirm with your initials electronically or in writing]**

First author: **Shoshana H Ballew**
Address: 2024 E. Monument St, Rm 2-609
Baltimore, MD 21287
Phone: 410-955-9917 Fax:
E-mail: sballew1@jhmi.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: **Shoshana H Ballew**
Address: 2024 E. Monument St, Rm 2-609
Baltimore, MD 21287
Phone: 410-955-9917 Fax:
E-mail: sballew1@jhmi.edu

3. Timeline:

Data analysis will start immediately. A manuscript is expected to be prepared within 6 months.

4. Rationale:

Reduced muscle mass is related to frailty and survival in older adults,[1-3] but changes in muscle mass are not routinely assessed in clinical medicine. Validated instruments to assess muscle mass in research studies include imaging, anthropometry, physical performance tests, and creatinine generation rate. We propose using physiologic relationships among the determinants of the serum creatinine concentration (Scr) (Figure 1) to estimate creatinine generation rate for use as a measure of muscle mass in epidemiologic studies that could be applicable in clinical practice.

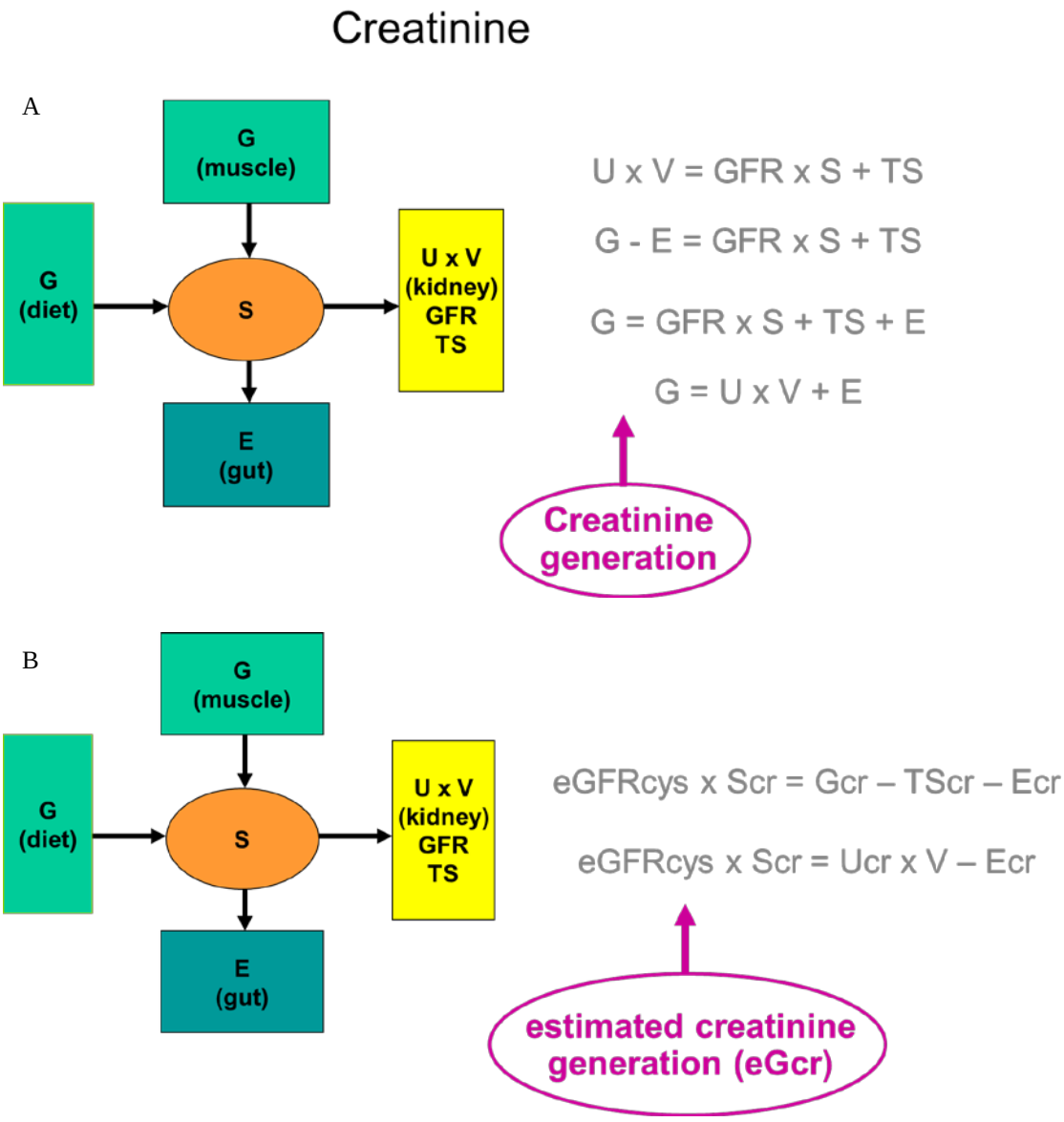

Figure 1 showing the physiologic relationships (A) and how these may be used to estimate creatinine generation rate (B). S = serum concentration of creatinine, in units of mass/volume; G = generation of creatinine, in units of mass/time; E = extra-renal elimination, in units of mass/time; UV = urinary excretion rate, in units of mass/time; TS = tubular secretion rate, in units of mass/time; GFR = glomerular filtration rate, in units of vol/time

In the steady state, urinary creatinine excretion rate is the difference between creatinine generation rate by muscle and diet minus extra-renal creatinine elimination rate by gut (Figure above). Urinary creatinine excretion rate is the sum of the rates of glomerular filtration and tubular secretion of creatinine. We hypothesize that the rates of extra-renal elimination and tubular secretion of creatinine are less variable than the rate of glomerular filtration of creatinine; thus, lower rates of glomerular filtration of creatinine may be related to lower rates of creatinine generation stemming from lower muscle mass and the onset of frailty in older adults.

The rate of glomerular filtration of creatinine is the product of the glomerular filtration rate (GFR) multiplied by serum creatinine concentration. There are equations for estimating GFR (eGFR) using either serum creatinine, serum cystatin C, or both.[4-6] We propose using eGFRcys rather than eGFRcr since eGFRcr can be inappropriately high in persons with low muscle mass, accompany correlate of the weakness and weight loss that are part of the definition of frailty. Alternatively, eGFRcys is less affected by muscle mass and is independent of serum creatinine. eGFRcys is also less affected by age and sex than eGFRcr and does not include race in the estimation.

In this study, we will estimate creatinine generation (eGcr) as the product of eGFRcys and serum creatinine (eGcr = eGFRcys x Scr) and determine its association with measures of muscle mass and frailty in a representative sample of the US population (NHANES) as well as with survival in an older community-based cohort (ARIC). We will also compare estimated creatinine generation with estimated urinary creatinine excretion rate, determined by formulas using age, sex, race, and clinical variables.

5. Main Hypothesis/Study Questions:
We hypothesize that estimated creatinine generation (eGcr) is related to measures of muscle mass, frailty, and survival in older adults.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design

We will conduct a cross-sectional study of the association between eGcr and markers of frailty syndrome at visit 5 in ARIC, as well as at survey time points when necessary variables are available in NHANES. We will also look at associations of eGcr at visit 5 with subsequent mortality in ARIC. In sensitivity analyses, we will also examine associations of eGcr at visits 2, 3 or 4 with mortality.

Exclusions

Participants with missing data on serum creatinine, cystatin C, or frailty syndrome at visit 5 will be excluded from the analyses. We will also exclude individuals with previous kidney failure requiring treatment. In the event that there is a substantial amount of missing data, we will determine its nature and will come to a consensus on the most appropriate way of dealing with it.

Variables

Estimated creatinine generation (eGcr): This will primarily be defined as eGFR calculated from serum cystatin C using the CKD-EPI equation (eGFRcys) multiplied by serum creatinine. In sensitivity analyses, we will use eGFR calculated from serum creatinine using the CKD-EPI equation.

Frailty syndrome. The ARIC Study Coordinating Center in collaboration with members of the ARIC Physical Function working group created a frailty variable based on the construct developed on the basis of data collected in the CHS.[1] Component elements of the frailty

construct were ascertained at ARIC Visit 5, with the exception of weight loss which was calculated based on Visit 5 and Visit 4 data (Table 1). The sample will be categorized into 3 groups: non-frailty, if none of the listed component phenotypes were present; pre-frailty, if one or two of the component phenotypes were present; and frailty, if three or more of the component phenotypes were present.

Table 1. Operationalization of the frailty construct in ARIC cohort	
Characteristic of Frailty	**Definition**
Unintentional weight loss	10% of unintentional weight loss from Visit 4 to Visit 5 or BMI<18.5kg/m2 at Visit 5
Low energy expenditure	Gender-specific 10th percentile rank of the Baecke leisure sports activity index
Low walking speed	Gender- and height-adjusted time in seconds used to walk 4 meters. Slowest speed was defined using the cutoff values established from CHS.
Low level of physical energy (Exhaustion)	Responded “some of the time” or “most of the time” to either of the following CESD questions: CES3 (I felt everything I did was an effort) or CES11 (I could not get “going”)
Low grip strength	Gender- and BMI-specific grip strength. Lowest grip strength was defined using the cutoff values established from CHS.

Other covariates of interest. Demographics (age, sex, race/ethnicity, education, income, marital status, and employment status at the most recent time data is available); other laboratory variables (albumin-to-creatinine ratio (ACR), urea nitrogen, bicarbonate, total cholesterol, glucose, calcium, phosphorus, albumin); health behaviors (smoking status, alcohol consumption, physical activity, and sedentary behavior); and comorbidities and health status variables (height, body weight, blood pressure, diabetes, history of cancer, history of peripheral arterial disease, coronary heart disease, heart failure, or stroke at or prior to visit 5, self-reported health status, anemia, inflammation, medication use).

Outcomes for follow-up. All-cause mortality. We may also examine cause-specific mortality in sensitivity analyses.

Statistical Analyses

Statistical tests will be two-sided and based on an α-level of 0.05. Descriptive statistics (proportions, means, and standard deviations) will be used to describe demographics, health behaviors, and risk factors and comorbidities by sex-specific quartiles of eGcr. Differences between groups will be assessed using chi-square tests for categorical variables and two sample t-tests or analysis of variance for continuous variables as is appropriate (if assumptions of these tests are not met, then non-parametric equivalents will be used).

The association between eGcr categories and frailty syndrome will be assessed using Poisson regression models to estimate prevalence ratios. We will compare models with adjustment for the following categories of variables:

Model 0: eGcr
Model 1: Model 0 + Demographics
Model 2: Model 0 + Model 1 + Health behaviors
Model 3: Model 0 + Model 1 + Model 2 + Comorbidities

We will test for interactions by age (older vs. younger), race/ethnicity (white vs. non-white), BMI (higher vs. lower), and smoking status (non-smoker vs. ever smoked) by including each variable as an interaction term in the models. The interaction term will be considered statistically significant at an α-level of 0.10. If significant interactions are observed, stratified results will be reported, although interpretations will be guided by the cell sizes and precision of effect estimates.

In longitudinal analyses, we will use Cox proportional hazards models with cubic splines to assess the relationship between eGcr and mortality, stratified by sex. We will use similar modeling adjustments:

Model 0: eGcr
Model 1: Model 0 + Demographics
Model 2: Model 0 + Model 1 + Health behaviors
Model 3: Model 0 + Model 1 + Model 2 + Comorbidities

Sensitivity analyses will stratify by eGFRcys as well as repeat analyses using eGFRcr for the calculation of eGcr.

Limitations

We will be unable to clearly establish the temporality of the observed associations due to the cross-sectional nature of the analyses with frailty. Also, for several important measures (e.g., smoking status, alcohol consumption, physical activity, and sedentary behavior), we will be relying entirely on self-reported information which may be associated with more misclassification than if objective measurements were obtained.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

_____ Yes ___X___ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
MP2303 manuscript: Ballew et al., Frailty, Kidney Function, and Polypharmacy: The Atherosclerosis Risk in Communities (ARIC) Study. *AJKD* 2017;69(2):228-236

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _X_ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* Mar 2001;56(3):M146-156.

2. Bandeen-Roche K, Seplaki CL, Huang J, et al. Frailty in Older Adults: A Nationally Representative Profile in the United States. *J Gerontol A Biol Sci Med Sci.* Nov 2015;70(11):1427-1434.
3. Shamliyan T, Talley KM, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. *Ageing Res Rev.* Mar 2013;12(2):719-736.
4. Inker LA, Eckfeldt J, Levey AS, et al. Expressing the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) cystatin C equations for estimating GFR with standardized serum cystatin C values. *Am J Kidney Dis.* Oct 2011;58(4):682-684.
5. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med.* Sep 5 2013;369(10):932-943.
6. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* May 5 2009;150(9):604-612.