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MODELING A PREDICTIVE ENERGY EQUATION SPECIFIC FOR MAINTENANCE HEMODIALYSIS

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Abstract

Background—Hypermetabolism is theorized in patients diagnosed with chronic kidney disease (CKD) on maintenance hemodialysis (MHD). We aimed to distinguish key disease-specific determinants of resting energy expenditure that can be used to create a predictive energy equation that more precisely establishes energy needs with the intent of preventing protein-energy wasting.

Materials and Methods—For this three-year, multi-site, cross-sectional study (N=116), eligible participants were diagnosed with CKD and on MHD for at least three months. Predictors for the model included weight, sex, age, c-reactive protein (CRP), glycosylated hemoglobin (A1C), and serum creatinine (SCr). The outcome variable was measured resting energy expenditure (mREE). Regression modeling was used to generate predictive formulas and Bland-Altman analyses to evaluate accuracy.

Results—The majority were male (60.3%), black (81.0%), non-Hispanic (76.7%) and 23% were 65 years or older. After screening for multi-collinearity, the best predictive model of mREE ($R^2=0.67$) included weight, age, sex, and CRP. Two alternative models with acceptable predictability ($R^2=0.66$) were derived with A1C or SCr. Using Bland-Altman analyses, the Maintenance Hemodialysis Equation with CRP included had the best precision with the highest proportion of participants' predicted energy expenditure classified as accurate (61.2%) and the lowest number of individuals with under- or over-estimation.

Conclusions—This study confirms disease-specific factors as key determinants of mREE in patients on MHD and provides a preliminary predictive energy equation. Further prospective research is necessary in order to test the reliability and validity of this equation across diverse populations of patients on MHD.

Introduction

In the US, one out of two patients diagnosed with chronic kidney disease (CKD) on maintenance dialysis will die within three years of initiating renal replacement therapy,

translating to a life expectancy that is less than one-third of the general population.¹ This is an important problem, given the nearly 700,000 individuals in the US who are affected, the high cost in human suffering and loss, and the expense to Medicare and private insurance. Causes for this high mortality rate are multifactorial and interdependent. Protein-energy malnutrition or wasting (PEW) is one independent risk factor for mortality.²⁻⁹ Disease progression leads to a decline in appetite and oral intake as well as physiological alterations in nutrient and energy metabolism.^{8,10-14} To offset the consequent sequelae of the disease process, nutritional care must be optimized. Effective nutritional intervention requires an appropriate predictive energy equation, based on an understanding of clinical factors, mechanisms, and an accurate determination of energy expenditure. Resting energy expenditure (REE), the largest component of the total energy expenditure,¹⁵ is most accurately measured in acute and chronic illness by indirect calorimetry (IC) utilizing a metabolic cart.¹⁶ Although measuring energy expenditure using IC is the preferred method in CKD, it is not routinely done in this practice setting¹⁷ because the methods required are cumbersome and the equipment used is cost-prohibitive.^{18,19} Typically, REE is estimated from a predictive formula that has been validated in other disease states or patient populations,^{20,21} and then extrapolated to CKD, with serious limitations.²² Despite the over 200 predictive energy equations currently published^{18,19,23} a “best practice” formula does not exist for CKD.²⁴ An initial investigation²⁵ has derived a disease-specific equation, but used heterogeneous treatment groups and a small sample (N=20) for validation.

As kidney disease progresses to end-stage renal failure, there are substantive alterations in energy expenditure that have not been clearly elucidated, and when coupled with a simultaneous decline in dietary intake, an energy imbalance is engendered.^{3,5,10-12,14,26,27} This discordance will eventually result in a suboptimal nutritional status and place the individual at an increased risk for morbidity and mortality. To further our understanding of energy expenditure in CKD, we hypothesized that there were several clinical factors that influence energy requirements.^{24,28-32} We recently published a preliminary predictive model that is disease-specific with better precision than some of the common formulas utilized, but we were not able to fully validate it for clinical use.³³ Subsequently, in a larger sample, we were able to measure REE (mREE) and identify key clinical factors similar to our pilot work. In addition, we were able to better refine and internally validate our predictive energy equation for patients diagnosed with stage 5 CKD on maintenance hemodialysis (MHD).

Methods

Participants

Participants, who were treated by MHD, were recruited from outpatient clinics associated with study teams from Rutgers University (RU), Case Western Reserve University (CWRU), and Pennsylvania State University-Hershey Medical Center (PSU-HMC). The detailed study protocol, comprising inclusion and exclusion criteria as well as the training calibration completed at the study sites, has been published elsewhere.³⁴ Informed consent, which followed Institutional Review Board (IRB) requirements at each research site (CWRU #08-12-37, PSU-HMC #40781EP and RU #2012001976), was obtained from those willing to participate and who met eligibility criteria.

Study Measurements

Each participant had testing completed on a non-hemodialysis treatment day at the designated research sites. Participants were instructed to fast 12 hours prior to the research appointment, but if not medically feasible, a 4-hour fast was deemed acceptable.

Measured Resting Energy Expenditure (mREE)

Energy expenditure was measured by IC using the Quark RMR® (Cosmed, Rome, Italy) at both RU and PS-HMC and the Vmax® Encore (CareFusion, Yorba Linda, California) metabolic cart at CWRU. For the purposes of this study, the Quark RMR® (newer IC device) was validated against the criterion standard, Deltatrac Metabolic Monitor (Sensormedics, Yorba Linda, CA), and was found to be of suitable precision for measuring REE.²¹ The Vmax® Encore and the Quark RMR were also tested for reliability, and were found to be comparable devices.³⁵ Additional details of the reliability testing completed have been reported previously.³⁴ The IC measurements were completed in accordance to evidence-based practice guidelines,¹⁸ and were instituted and followed at each research institution in order to minimize measurement error.³⁵ The 5-minute steady state protocol followed the methodology published by Olejnik et al (2016).³⁴ To calculate mREE, we used the Weir equation:³⁶

$$\text{mREE} = [(3.94 * \text{VO}_2) + (1.11 * \text{VCO}_2)] * 1.44(10)$$

Laboratory Assays

Blood samples were drawn at each clinical site after all other clinical measurements were obtained on a non-hemodialysis treatment day, or immediately pre-dialysis. When blood could not be drawn, respective values were abstracted from the medical record (MR) for their most recent pre-dialysis monthly chemistries. Timing of the blood draw (non-hemodialysis vs. pre-dialysis) was tested for equivalence in both high-sensitivity C-reactive protein (CRP; $p=0.985$) and serum creatinine (SCr; $p=0.095$). Following centrifugation, serum for blood urea nitrogen (BUN), SCr, albumin (ALB), CRP, and plasma for intact parathyroid hormone (iPTH), was obtained, aliquoted, and frozen at -80°C . Whole blood was aliquoted and frozen for glycosylated hemoglobin (A1C). A complete blood count with differential was performed on fresh whole blood in local laboratories or values were obtained from recent monthly blood work recorded in the participant's MR. Inter-plate and inter-run variation was assessed through comparison of standard curves and control values.

Statistical Methods

Data entered into Research Electronic Data Capture (RedCap®; Vanderbilt University, Nashville, TN) from the three study sites were downloaded for import into the statistical programs used for the analysis (Stata 14, College Station, TX; SPSS 24, Chicago, IL). Data were examined for veracity by the study team and questions regarding particular measurements were checked against paper documentation.

Missing Values and Data for Analyses

The analysis plan called for randomly splitting the data set into a model creation subsample and a model validation subsample. While the initial recruitment plan had assumed some amount of missing data, the final number of subjects with complete data was lower than anticipated (n=95). The original power analysis had called for n=60 to generate the initial equation and n=95 for the validation component. We determined that even after imputation (n=116), splitting the data set risked over fitting and so a decision was made to analyze the entire sample.

To maximize data available for analyses, missing values were imputed. We first determined that missing values were not monotonic³⁷ and were not related to measures of patient disease burden. Multivariate normal (MVN) imputation was completed using Stata 14³⁸ with 50 replications. Though values on the predictor variables were imputed based on a range of demographic, clinical and lab variables, a solution had to be forced due to missing values on the non-imputed variables. This decreased our confidence in the reliability of the imputed values. We then imputed values using multiple regression. Because imputation by multiple regression can reduce variance,³⁹ we ran a sample multivariate model predicting mREE to compare coefficients and standard errors on three samples: (1) subjects with complete data (n=95), (2) subjects with missing values imputed via MVN (n=109), and (3) subjects with values imputed via multiple regression (using the same non-imputed variables as were used in the MVN but using pair-wise deletion to retain as much information as possible) (n=120). We then compared coefficients and standard errors of the three models (Supplemental Material; Table S1) to determine whether there were any serious discrepancies between parameters for the different models. Standard errors in the regression imputed model did not vary by greater than 6% from either the MVN or complete data models, hence, values from the multivariate regression imputed model were used. Because of device malfunction on one day of study, four cases had to be removed, leaving a final sample of 116 participants. The demographic and clinical characteristics of the four cases removed were similar to the larger sample.

Development of Predictive Models

The general procedure for developing the predictive model is described in Byham-Gray, et al., 2014.³³ Briefly, a list of potential predictors was developed based on prior research.^{28,30,40} Variables were then screened for bivariate linear relationships with 5-minute mREE measures, and those with a correlation value of $p < 0.15$ were identified as potential predictors. Bivariate relationships among the selected predictors were then examined, and when they were highly correlated ($r \geq .7$), the potential predictor with the strongest relationship to mREE was selected. All continuous variables identified as potential predictors at this stage were then screened for quadratic relationships with mREE using a curve fitting procedure. Linear and quadratic models were compared to determine whether the quadratic model provided a substantial improvement over the linear model. Multiple regression was used to evaluate the contribution of the potential predictors from the above procedure. All final models were assessed for collinearity, functional form, normality of errors and homoscedasticity.

Evaluation of Accuracy of the Predictive Models

Bland-Altman analyses⁴¹ were used to evaluate the accuracy of the predicted REE values relative to mREE. Mean model bias and 95% confidence intervals around mean bias of each model were computed. Standard errors of the three bias estimates were computed and accuracy of the bias estimates are reported.

Results

One-hundred-sixteen participants were available for analysis (Figure 1). The majority were male (60.3%, n=70), black (81.0%, n=94) and non-Hispanic (76.7%, n=89) (Table 1). The mean age of participants was 56.32 ± 11.92 years, with 23.3% (n=27) at least 65 years old. Hypertension (40.5%, n=47) and diabetes (37.1%, n=43) were the two leading etiologies of kidney disease reported. The average dialysis vintage was just over five years (61.64 ± 69.93 months). Mean weight was 87.01 ± 20.17 kg and BMI was 30.37 ± 6.63 . Average CRP values were greater than 10 mg/dl and ALB levels were within normal limits (4.18 ± 0.44 g/dl). iPTH ranged from as low as 10.90 to as high as 4315.00 pg/mL. Mean A1C values were <7.0%.

Average mREE was 1522.59 ± 334.92 kcal. The distribution of mREE was slightly skewed in the sample, due largely to the presence of four outliers which were confirmed to be accurate. Transforming the outcome variable would dramatically decrease the clinical utility of the final equation and with no clinical justification for dropping these cases, such outliers were retained in the model.

Results of Models to Predict mREE

Following the above procedure, in addition to one anthropometric measure (e.g., weight) age, sex (coded 0=female, 1=male), and CRP levels were identified as the strongest predictors of mREE (Table 2). A1C and SCr were the next strongest predictors of mREE. All potential predictors were evaluated for non-linear relationships with mREE. None of the quadratic relationships between the above variables and mREE improved model fit by >3%. In the interest of creating models that would be both accurate as well as useful by clinicians, no quadratic terms were included in the models.

Because a particular lab value may not be available in every clinical situation, three models were constructed—differing according to the lab value included in the base model (e.g., CRP, A1C or SCr). All models significantly predicted mREE ($p < 0.001$) (Table 3). The model including both weight and CRP had the highest proportion of variance explained ($R^2 = .67$), with the models including weight and SCr or A1C being equivalent ($R^2 = .66$).

Maintenance Hemodialysis Equation (MHDE-CRP 2016)

The best predictive model for males and females when CRP is available is:

$$\text{Male REE} = 1027.8 - (5.19 * \text{Age}) + (9.67 * \text{Weight}) + (2.71 * \text{CRP})$$

$$\text{Female REE} = 820.47 - (5.19 * \text{Age}) + (9.67 * \text{Weight}) + (2.71 * \text{CRP})$$

Where age (yrs), post-dialysis weight (kg), and CRP (mg/dl)

If CRP is not available, then either A1C or SCr may be substituted into the model as follows:

MHDE-A1C (2016):

$$\text{Male REE} = 1128.06 - (4.62 * \text{Age}) + (10.33 * \text{Weight}) - (21.79 * \text{A1C})$$

$$\text{Female REE} = 886.7 - (4.62 * \text{Age}) + (10.33 * \text{Weight}) - (21.79 * \text{A1C})$$

Where age (yrs), post-dialysis weight (kg), and A1C (%)

MHDE-SCr (2016):

$$\text{Male REE} = 1024.41 - (4.90 * \text{Age}) + (10.21 * \text{Weight}) - (3.25 * \text{SCr})$$

$$\text{Female REE} = 802.00 - (4.90 * \text{Age}) + (10.21 * \text{Weight}) - (3.25 * \text{SCr})$$

Where age (yrs), post-dialysis weight (kg), and SCr (mg/dl)

Evaluation of REE Equations

While none of the models demonstrated statistically significant bias in predicted REE (kcal/day) relative to measured (all $p > 0.05$), the model that included A1C showed a slight mean underestimate (-77.35 ± 184.79) of mREE (Table 4 and Figure 2). Models with CRP and SCr had a mean bias of zero. The 95% confidence intervals of the mean bias were all approximately equal. When $\pm 10\%$ of REE (± 152) is used as a threshold for accuracy, the model with CRP had the highest proportion of subjects classified as accurate (61.2%, $n=71$), with both A1C and SCr models classifying 56.9% accurately.

Discussion

In comparison to healthy controls, the energy expenditure of individuals on MHD is significantly higher, placing them at greater risk for hypercatabolism, and therefore protein-energy wasting (PEW).^{11,30,42,43} To minimize such risk, research efforts aimed at more fully understanding the contributors of energy expenditure are critical. On the basis of our findings, we continue to support the hypothesis that the addition of laboratory data produce better fitting models of mREE among patients on MHD than using demographic and anthropometric characteristics alone as is commonly done in predictive formulas for healthy populations.^{44,45} Hence, we were able to explain a greater proportion of the variance in mREE among patients diagnosed with CKD, with a higher degree of precision than any of the other earlier investigations.^{25,33} In so doing, we confirmed similar predictors of mREE from our pilot study, and were able to create and internally validate a model within a larger sample of patients on MHD.

As is evident in the research literature of non-CKD and CKD samples, demographic and anthropometric characteristics are predictors of mREE.^{19,44-46} Since the primary goal of our research is to create a predictive model of REE that can be easily used in clinical practice, we chose weight as the main anthropometric parameter, as it is routinely collected within the dialysis clinic. While BIA data and/or FFM estimates derived from these data can be applied, we did not include them within our procedures for developing a model with the greatest clinical utility, and hence, replicated our earlier methodology.³⁴ Thus, in our sample,

weight remained as the strongest predictor of mREE and therefore is a reasonable estimate for metabolically active tissue or FFM.⁴⁷ Since a large proportion of the sample had BMIs 30, it would be instructive in a future investigation with a larger, robust dataset, to stratify by BMI category to determine whether adiposity provides any additional explanation for mREE. Nonetheless, weight was the anthropometric measure chosen for the predictive models constructed in this study based on its superior clinical utility. As expected, age and sex were contributors of mREE, which is congruent with general populations.^{44,45}

Factors that are proposed to impact energy expenditure beyond the traditional ones and are specific to CKD include parathyroid hormone concentrations, inflammation, and the presence of diabetes.^{30,31,48} In two separate studies, inflammation was associated with an acceleration in energy expenditure among CKD patients.^{40,48} Similar to our preliminary findings,³³ this sample of patients on MHD were largely inflamed, and the CRP levels remained as a strong predictor of mREE. As such, our results suggest that the REE among these patients is elevated and any of the existing predictive energy equations that do not account for these factors could grossly underestimate energy determinations with potentially harmful side-effects. Of the three laboratory values examined in this analysis, CRP most improved the fit of the model.

In studying the effects of co-morbid conditions on energy expenditure, Pupim and associates²⁸ reported that the unadjusted mREE in patients with diabetes was significantly higher than in patients without disease. Theorizing that hyperglycemia may be a significant contributor to energy expenditure in CKD, we included A1C as a parameter within our study. Thus, we replaced CRP (which may not be routinely collected within a dialysis facility) with A1C to examine how it would perform in our predictive model. The presence of diabetes did assist in explaining the variance in the mREE. However, A1C may have been a stronger predictor if there were a larger proportion of participants with levels above 7%. Further study into the relationship between glycemia and energy expenditure is warranted.

SCr may reflect muscle mass in healthy groups. Since creatinine is excreted by the kidney, it is an imprecise surrogate marker in CKD. Nonetheless, serial monitoring and tailored acceptable limits of SCr in stage 5 CKD may provide additional insight into the body habitus.^{3,49} Because SCr values are routinely collected for the purpose of determining dialytic adequacy and protein nutrition, we chose to evaluate its ability to predict mREE in this sample. In our predictive modeling, SCr continues to be an alternate parameter that may be used when either CRP or A1C are unavailable or missing.³³ SCr is convenient, easily accessible, and its inclusion improved the practicality of the predictive model. Therefore, data once again support the need to have CKD specific parameters when trying to explain mREE in this population.

Moderate to severe secondary hyperparathyroidism has been reported as one of the strongest determinants of mREE in a multivariate linear regression analysis.³⁰ Conversely, iPTH levels were not a significant contributor for mREE in our sample. While our results may seem counterintuitive, the findings are likely more related to the use of imputed values for the missing data. In light of the metabolic compromise exhibited during hyperparathyroidism, we continue to hypothesize that elevated iPTH levels are expected to

be a contributor to the overall disease state and should be accounted for in the overall explanation for energy expenditure. Hence, this disease-specific parameter merits further scientific inquiry.

In terms of its overall precision, our equation explains more of the variance of mREE than our earlier model in a similar MHD population.³³ We also gained a higher proportion of participants for whom the equation “accurately” estimated REE which is higher than other commonly reported equations, even in general populations.^{33,45,46} Nonetheless, there are individuals who fell outside the band of acceptability, and additional exploration into improving the bias is warranted, and limits the broad application of such findings without further inquiry. Using a larger, diverse dataset, and conducting a more comprehensive analysis of the characteristics among individuals for which the model may not “fit” as well will afford a greater understanding of energy expenditure in CKD. Also, there still remains approximately 40% of the variance of the mREE that has not been explained by current models. As such, there are other factors existing in patients on MHD that have not yet been identified. Hence, completing future investigations focused on these innovative approaches would potentially lead to a more tailored mechanism for determining REE in this unique population and thereby support precision medicine.

While traditional IC measurement remains impractical for most clinical settings and the need for more precise modeling of energy expenditure is still of considerable research interest, there are a new generation of IC devices, as described by the *International Multicentric Study Group for Indirect Calorimetry Study Group*,⁵⁰ that may prove to be easier, less expensive and potentially useful within a myriad of inpatient and outpatient areas. Future research may determine whether these newer versions offer better clinical utility than either traditional IC devices or disease-specific predictive energy equations.

In conclusion, this study confirms disease-specific factors as key determinants of mREE in patients on MHD and provides a preliminary predictive energy equation. Further prospective research is necessary in order to test the reliability and validity of this equation across diverse populations of patients on MHD. Despite our findings, there are a few limitations that motivate us to be cautious in the interpretation of the results. We have limited generalizability due to the rather homogeneous sample of patient demographics and disease acuity (e.g., mostly stable patients on MHD). While more clinically useful, the use of weight instead of FFM derived from BIA data may have inherent errors, and future research should integrate such data using more sophisticated analytic techniques. Lastly, the use of multiple imputations for missing data may represent a conservative estimate of potential predictors in the regression modeling conducted and may mask the contribution of other factors that determine energy expenditure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. United States Renal Data System. USRDS annual data report: Epidemiology of Kidney Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2015. 2015
2. Lowrie EG, Lew NL. Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis.* 1990; 15:458–482. [PubMed: 2333868]
3. National Kidney Foundation. Kidney Disease Dialysis Outcome Quality Initiative (K/DOQI) clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis.* 2000; 35(Suppl 2):S1–S140. [PubMed: 10895784]
4. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys M. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance dialysis patients. *Am J Kidney Dis.* 2001; 38(6):1251–63. [PubMed: 11728958]
5. Pifer T, McCullough KP, Fort FK, Goodkin DA, Maroni BJ, Held PJ, Young EW. Mortality risk in hemodialysis patients and changes in nutritional indicators: Dialysis Outcomes Practice Patterns Study (DOPPS). *Kidney Int.* 2002; 62(4):2238–45. [PubMed: 12427151]
6. de Araújo ICKM, Draibe SA, Canziani ME, Manfredi SR, Avesani CM, Sesso R, Cuppari L. Nutritional parameters and mortality in incident hemodialysis patients. *J Renal Nutr.* 2006; 16:27–35.
7. Fouque D, Kalantar-Zadeh K, Kopple JD, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen GA, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevinho-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int.* 2008; 73(4):391–8. [PubMed: 18094682]
8. Bossola M, Giungi S, Luciani G, Tazza L. Appetite in chronic hemodialysis patients: A longitudinal study. *J Ren Nutr.* 2009; 19(5):372–379. [PubMed: 19540136]
9. Lopes AA, Bragg-Gresham JL, Elder SJ, Ginsberg N, Goodkin DA, Pifer T, Lamiere N, Marshall MR, Asano Y, Akizawa T, Pisoni R, Young EW, Port FK. Independent and joint associations of nutritional status indicators with mortality risk among chronic hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Ren Nutr.* 2010; 20(4):224–34. [PubMed: 20060319]
10. Burrowes J, Larive B, Chertow GM, Cockram D, Dwyer JT, Greene T, Kusek JW, Leung J, Rocco MV. Self-reported appetite, hospitalization and death in hemodialysis patients: Findings from the Hemodialysis (HEMO) Study. *Nephrol Dial Transplant.* 2005; 20(12):2765–74. [PubMed: 16204298]
11. Ikizler TA, Wingard RL, Sun M, Harvell J, Parker RA, Hakim RM. Increased energy expenditure in hemodialysis patients. *J Am Soc Nephrol.* 1996; 7(12):2646–2653. [PubMed: 8989743]
12. Kuhlmann U, Schwickardi M, Trebst R, Lange H. Resting metabolic rate in chronic renal failure. *J Ren Nutr.* 2001; 11:202–206. [PubMed: 11680000]
13. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, Mitch WE, Price SR, Wanner C, Wang AY, Ter Wee P, Franch HA. Etiology of the protein- energy wasting syndrome in chronic kidney disease: A consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr.* 2013; 23(2):77–90. [PubMed: 23428357]

14. Lopes A, Elder SJ, Ginsberg N, Andreucci VE, Cruz JM, Fukuhara S, Mapes O, Saito A, Pisoni RL, Saran R, Port FR. Lack of appetite in hemodialysis patients—associations with patient characteristics, indicators of nutritional status, and outcomes in the international DOPPS. *Nephrol Dial Transplant*. 2007; 22(12):3538–46. [PubMed: 17893106]
15. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, D.C.: National Academy Press; 2002.
16. Academy of Nutrition and Dietetics, Evidence Analysis Library. Evidence-Based Guidelines for Critical Illness 2012. Available at: <http://www.andeal.org/topic.cfm?menu=5302&cat=4800>. Accessed October 1, 2016
17. Schatz S, Pagenkemper J, Beto J. Body Weight Estimation in Chronic Kidney Disease: Results of a Practitioner Survey. *J Ren Nutr*. 16(3):283–286.
18. Fullmer S, Benson-Davies S, Earthman CP, Frankenfield DC, Gradwell E, Lee PS, Piemonte T, Trabulsi J. Evidence analysis library review of best practices for performing indirect calorimetry in healthy and non-critically ill individuals. *J Acad Nutr Diet*. 2015; 115(9):1417–1446.e1412. [PubMed: 26038298]
19. Frankenfield D, Hise M, Malone A, Russell M, Gradwell E, Compher C. Prediction of resting metabolic rate in critically ill adult patients: results of a systematic review of the evidence. *J Am Diet Assoc*. 2007; 107(9):1552–1561. [PubMed: 17761232]
20. Frankenfield DCA, Alam S, Cooney RN. Analysis of estimation methods for resting metabolic rate in critically ill adults. *J Parenter Enteral Nutr*. 2009; 33(1):27–36.
21. Ashcraft CM, Frankenfield DC. Validity Test of a New Open-Circuit Indirect Calorimeter. *J Parenter Enteral Nutr*. 2015; 39(6):738–742.
22. Mafra D, Deleaval P, Teta D, Cleaud C, Perrot M-J, Rognon S, Thevenet M, Arkouche W, Jolivo A, Fouque D. New measurements of energy expenditure and physical activity in chronic kidney disease. *J Ren Nutr*. 2009; 19(1):16–9. [PubMed: 19121764]
23. Kamimura MA, Avesani CM, Bazanelli AP, Baria F, Draibe SA, Cuppari L. Are prediction equations reliable for estimating resting energy expenditure in chronic kidney disease patients? *Nephrol Dial Transplant*. 2011; 26(2):544–550. [PubMed: 20663791]
24. Cuppari L, Avesani CM. Energy requirements in patients with chronic kidney disease. *J Ren Nutr*. 2004; 14(3):121–126. [PubMed: 15232789]
25. Vilar E, Machado A, Garrett A, Kozarski R, Wellsted D, Farrington K. Disease-specific predictive formulas for energy expenditure in the dialysis population. *J Ren Nutr*. 2014; 24(4):243–251. [PubMed: 24788307]
26. Kopple J, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, Scherch LK, Schulman G, Wang SR, Zimmer GS. Relationship between nutritional status and the glomerular filtration rate: Results from the MDRD Study. *Kidney Int*. 2000; 57:1688–1703. [PubMed: 10760105]
27. Panesar A, Agarwal R. Resting energy expenditure in chronic kidney disease: Relationship with glomerular filtration rate. *Clin Nephrol*. 2003; 59(5):360–366. [PubMed: 12779098]
28. Pupim L, Flakoll PJ, Majchrzak KM, Guy DLA, Stenvinkel P, Ikizler TA. Increased muscle protein breakdown in chronic hemodialysis patients with type 2 diabetes mellitus. *Kidney Int*. 2005; 68(4):1857–65. [PubMed: 16164664]
29. Skouroliaou M, Stathopoulou M, Koulouri A, Giannopoulou I, Stamatiades D, Stathakis C. Determinants of resting energy expenditure in hemodialysis patients, and comparison with healthy subjects. *J Ren Nutr*. 2009; 19(4):283–290. [PubMed: 19539183]
30. Cuppari L, Avesani CM, Santos NSJ, Kamimura MA, Draibe SA. Increased resting energy expenditure in hemodialysis patients with severe hyperparathyroidism. *J Am Soc Nephrol*. 2004; 15:2933–2939. [PubMed: 15504947]
31. Avesani CM, Cuppari L, Silva AC, Sigulem DM, Cendoroglo M, Sesso R, Draibe SA. Resting energy expenditure in pre-dialysis diabetic patients. *Nephrol Dial Transplant*. 2001; 16:556–560. [PubMed: 11239031]
32. Kamimura MA, Draibe SA, Avesani CM, Canziani ME, Colugnati FA, Cuppari L. Resting energy expenditure and its determinants in hemodialysis patients. *Eur J Clin Nutr*. 2007; 61(3):362–367. [PubMed: 16943847]

33. Byham-Gray L, Parrott JS, Ho WY, Sundell MA, Ikizler TA. Development of predictive energy equation-A pilot study. *J Ren Nutr.* 2014; 24(1):32–41. [PubMed: 24355819]
34. Olejnik, L; Peters, E; Parrott, JS; Marcus, A; Brody, R; Hand, R; Fiutem, JJ; Byham-Gray, L. Abbreviated steady state intervals for measuring resting energy expenditure in patients on maintenance hemodialysis. *J Parenter Enteral Nutr.* 2016. Epub:
35. Frankenfield DC, Ashcraft CM, Wood C, Chinchilli VM. Validation of an indirect calorimeter using n-of-1 methodology. *Clin Nutr.* 2016; 35(1):163–8. [PubMed: 25707909]
36. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *Nutrition.* 1990; 6(3):213–21. [PubMed: 2136000]
37. Potthoff Richard F, et al. Can One Assess Whether Missing Data are Missing at Random in Medical Studies? *Statistical Methods in Medical Research.* 15(3)2006; :213–234. [PubMed: 16768297]
38. Carlin JB, Galati JC, Royston P. A new framework for managing and analyzing multiply imputed data in stata. *Stata Journal.* 2008; 8(1):49–67.
39. Hawthorne G, Elliott P. Imputing cross-sectional missing data: Comparison of common techniques. *Australian & New Zealand Journal of Psychiatry.* 2005; 39(7):583–590. [PubMed: 15996139]
40. Mafra D, Deleaval P, Teta D, Cleaud CR, Arkouche W, Jolivot A, Fouque D. Influence of inflammation on total energy expenditure in hemodialysis patients. *J Ren Nutr.* 2011; 21(5):387–393. [PubMed: 21239181]
41. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986; 1(8476):307–310. [PubMed: 2868172]
42. Skouroliahou M, Stathopoulou M, Koulouri A, Giannopoulou I, Stamatiades D, Stathakis C. Determinants of resting energy expenditure in hemodialysis patients, and comparison with healthy subjects. *J Ren Nutr.* 2009; 19(4):283–290. [PubMed: 19539183]
43. Neyra R, Chen KY, Sun M, Shyr Y, Hakim RM, Ikizler TA. Increased resting energy expenditure in patients with end-stage renal disease. *J Parenter Enteral Nutr.* 2003; 27(1):36–42.
44. Harris, JABF. A biometric study of basal metabolism in man. Washington, DC: Carnegie Institution of Washington; 1919.
45. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr.* 1990; 51(2):241–247. [PubMed: 2305711]
46. Frankenfield DC. Bias and accuracy of resting metabolic rate equations in non-obese and obese adults. *Clin Nutr.* 2013; 32(6):976–982. [PubMed: 23631843]
47. Frankenfield D, Rowe WA, Cooney RN, Smith JS, Becker D. Limits of body mass index to detect obesity and predict body composition. *Nutrition.* 2001; 17:26–30. [PubMed: 11165884]
48. Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. *Am J Clin Nutr.* 2005; 82(4):801–5. [PubMed: 16210709]
49. Patel S, Molnar MZ, Tayek JA, Joachim HI, Noori N, Benner D, Heymsfield S, Kopple JD, Kovesdy CP, Kalantar-Zadeh K. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. *J Cachexia Sarcopenia Muscle.* 2013; 4:19–29. [PubMed: 22777757]
50. Oshima, T; Berger, MM; DeWaele, E; Guttormsen, AB; Heidegger, C-P; HiesmayerSinger, P; Wernerman, J; Pichard, C. Indirect calorimetry in nutritional therapy. A position paper by the International Multicentric Study Group for Indirect Calorimetry study group. *Clin Nutr.* 2016. Epub:

Clinical Relevancy Statement

This study aids clinicians by distinguishing key disease-specific characteristics of resting energy expenditure among patients on maintenance hemodialysis. Developing predictive energy equations using methods that allow for the adjustment of clinically relevant factors appear to more precisely establish energy needs in this vulnerable group than formulas derived in the healthy populations.

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Figure 1.

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Figure 2.

a. Bland-Altman Analysis of the MHDE-CRP in Comparison to the Measured Resting Energy Expenditure in a Sample of Maintenance Hemodialysis Patients from the North East Region of the United States.

b. Bland-Altman Analysis of the MHDE-A1C in Comparison to the Measured Resting Energy Expenditure in a Sample of Maintenance Hemodialysis Patients from the North East Region of the United States.

c. Bland-Altman Analysis of the MHDE-SCr in Comparison to the Measured Resting Energy Expenditure in a Sample of Maintenance Hemodialysis Patients from the North East Region of the United States.

Small dashed lines are the $\pm 10\%$ REE limits of agreement. Wide dashed lines are the $\pm 95\%$ CI of the mean bias. The solid center line is the mean bias.

Table 1

Demographic, Anthropometric, and Clinical Characteristics for a Sample of Maintenance Hemodialysis Patients from Three Research Institutions within the Northeast Region of the United States (N=116)

	N	Percent	Mean±SD	Min/Max
Demographics				
Sex	116			
Male	70	60.3		
Race	116			
White	22	19.0		
Black	94	81.0		
Ethnicity	116			
Hispanic	10	8.6		
Non-Hispanic	89	76.7		
Unknown	17	14.7		
Age	116		56.32±11.92	21.50/80.74
At least 65	27	23.3		
Etiology of CKD				
Diabetes	43	37.1		
Hypertension	47	40.5		
GLN	4	3.4		
PKD	4	3.4		
ESRD/unspecified	27	23.3		
AIDS/HIV-related	6	5.2		
Cancers	1	0.9		
AKI	5	4.3		
Systemic diseases	2	1.7		
Miscellaneous	5	4.3		
Dialysis Vintage (Months)	114		61.64±69.93	3.00/411.00
Anthropometrics				
Weight (kg)	116		87.01±20.17	47.10/150.80
BMI	116		30.37±6.63	18.74/50.77
Clinical Characteristics				
mREE (kcal/day)	116		1522.59±334.92	880.55/2448.05
Laboratory Parameters				
SCr (mg/dl)	116		8.14±3.20	0.83/16.93
BUN (mg/dl)	116		41.37±18.08	8.80/102.20
ALB (g/dl)	116		4.18±0.44	3.10/5.44
CRP (mg/dl)	116		10.13±14.65	0.10/93.99
PTH (pg/ml)	115		478.45±631.96	10.90/4315.00
A1C (%)	109		6.06±1.22	4.80/11.60

Footnotes: Chronic Kidney Disease, CKD; Glomerulonephritis, GLN; Polycystic Kidney Disease, PKD; End-Stage Renal Disease, ESRD; Auto-Immune Deficiency Syndrome, AIDS; Human Immunodeficiency Virus, HIV; Acute Kidney Injury, AKI; Body Mass Index, BMI; Measured Resting Energy Expenditure, mREE; Serum Creatinine, SCr; Blood Urea Nitrogen, BUN; Serum Albumin, ALB; C-Reactive Protein, CRP; Parathyroid Hormone, PTH; Glycosylated Hemoglobin, A1C.

Conversion factors for units: SCr in mg/dl to $\mu\text{mol/L}$, $\times 88.4$; BUN in mg/dl to mmol/L , $\times 0.357$;

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Table 2

Potential Predictor Variables by Strength of Correlation with mREE in a Sample of Maintenance Hemodialysis Patients from the Northeast Region of the United States (N=114)

Variable	r or rho	p value
Weight (kg)	0.73	<0.001
Sex	0.50	<0.001
BMI (kg/m ²)	0.48	<0.001
Age (yrs)	−0.36	<0.001
CRP (mg/dl)	0.32	0.001
A1C (%)	−0.18	0.065
SCr (mg/dl)	0.17	0.076
iPTH (pg/ml)	0.15	0.104
ALB (g/dl)	0.09	0.320
BUN (mg/dl)	−0.07	0.428

Footnotes: Body Mass Index, BMI; Serum Creatinine, SCr; Blood Urea Nitrogen, BUN; Serum Albumin, ALB; C-Reactive Protein, CRP; Parathyroid Hormone, PTH; Glycosylated Hemoglobin, A1C.

Conversion factors for units: SCr in mg/dl to $\mu\text{mol/L}$, $\times 88.4$; BUN in mg/dl to mmol/L , $\times 0.357$;

Table 3

Predictive Models for Measured Resting Energy Expenditure (kcal/day) in a Sample of Patients on Maintenance Hemodialysis in the Northeast Region of the United States (N=116)

	Model 1: MHDE-CRP	95% CI	Model 2: MHDE-A1C	95% CI	Model 3: MHDE-SCr	95% CI
	Coefficient		Coefficient		Coefficient	
Constant	820.47	552.53	886.70	567.16	802.00	512.23
Age (yrs)	-5.19	-8.30	-4.62	-7.84	-4.90	-8.09
Sex	207.33	131.56	214.36	135.81	222.41	145.37
Weight (kg)	9.67	7.75	10.33	8.38	10.21	8.31
CRP (mg/dl)	2.71	0.15				
A1C (%)			-21.79	-52.50		
SCr (mg/dl)				8.93	-3.25	-15.02
Adj. R square	0.67		0.66		0.66	

Footnote: Maintenance Hemodialysis Equation with CRP, MHDE-CRP; Maintenance Hemodialysis with A1C, MHDE-A1C; Maintenance Hemodialysis with Serum Creatinine, MHDE-SCr; Serum Creatinine, SCr; Blood Urea Nitrogen, BUN; C-Reactive Protein, CRP; Glycosylated Hemoglobin, A1C.

Conversion factors for units: SCr in mg/dl to $\mu\text{mol/L}$, $\times 88.4$; BUN in mg/dl to mmol/L , $\times 0.357$;

Table 4

Direction of Agreement and Residual Bias for Three Predictive Models for Measured Resting Energy Expenditure (kcal/day) in a Sample of Maintenance Hemodialysis Patients from the Northeast Region of the United States (N=116)

	Models		
Agreement Estimates	MHDE-CRP	MHDE-A1C	MHDE-SCr
UCI of Limit UCI	400.65	385.92	407.94
Bias Limit UCI	370.27	354.83	377.01
LCI of Limit UCI	339.89	323.75	346.08
UCI of Bias	17.54	10.60	17.86
Mean Bias	0.00	-7.35	0.00
LCI of Bias	-17.54	-25.30	-17.86
UCI of Limit LCI	-339.89	-338.45	-346.08
Bias Limit UCI	-370.27	-369.53	-377.01
LCI of Limit LCI	-400.65	-400.62	-407.94

Footnotes: Maintenance Hemodialysis Equation with CRP, MHDE-CRP; Maintenance Hemodialysis with A1C, MHDE-A1C; Maintenance Hemodialysis with Serum Creatinine, MHDE-SCr; Upper Confidence Interval, UCI; Lower Confidence Interval, LCI.