RESEARCH LETTER

Volume and Body Composition in Hemodialysis Patients: A Bioimpedance Study Assessing Differences by Sex

To the Editor:

Individuals with kidney disease receiving maintenance hemodialysis exhibit improved survival with higher baseline body mass index and weight gain over time.[1] This reversal of risk factors compared with the general population (often misnamed "reverse epidemiology") has been substantiated by metrics of body composition obtained through bioimpedance spectroscopy.[2] Specifically, bioimpedance spectroscopy data have indicated survival was optimal with a predialysis lean tissue index (LTI) of 15-20 kg/m^2 and fat tissue index (FTI) of 4-15 kg/m^2.[3] Bioimpedance-derived estimates of predialysis fluid status are also associated with increased mortality when exceeding 2.5 L absolute volume overload (VO) and 15% relative VO as a percentage of extracellular water.[4] Although reference individuals for LTI and FTI were age- and sex-matched, those for VO were not.[4,5] In light of current efforts to better understand sex discrepancies in kidney disease patients, we aimed to explore whether there are differences in predialysis body composition and fluid status between male and female patients on hemodialysis.[6]

We retrospectively analyzed predialysis bioimpedance measurements conducted in patients on maintenance hemodialysis between November 2022 and January 2023 at the Vienna Dialysis-Center (a tertiary care facility in Vienna, Austria). Patients were measured with the Body Composition Monitor (Fresenius Medical Care) and the Cella (Cella Medical) bioimpedance spectroscopy devices in standard wrist-to-ankle setups using pregelled electrodes. Detailed methodology and further results are provided in Items S1-S3.

In November 2022, the Vienna Dialysis-Center cared for 304 patients (285 patients on regular twice or thrice weekly hemodialysis, 11 undergoing in-hospital treatment, 8 on vacation). Predialysis bioimpedance data from 159 patients were available for initial evaluation. After excluding erroneous measurements (Fig S1), 137 patients remained for sex comparisons, 85 (62.0%) of whom were men and 52 (38.0%) were women. Study population data and bioimpedance data from the Body Composition Monitor are shown overall and stratified by sex in Table 1. Predialysis VO (higher in men), LTI (higher in men), and FTI (higher in women) differed significantly between sexes, whereas relative VO did not. The proportion of patients within LTI measurements of 15-20 kg/m^2 (the range with optimal survival) differed significantly between men and women (27.1% vs 7.7%, $P < 0.01$), but there was no difference for the above-mentioned thresholds of absolute and relative VO or FTI (Figs 1 and S2).[3,4] Body Composition Monitor and Cella devices differed significantly in all parameters (Table S1 and Figs S3-S7).

In summary, we found significant differences between male and female patients in predialysis VO, LTI, and FTI not only in absolute terms but also in the proportion of patients considered to be "in-range" of LTI. Although higher LTI was previously associated with lower mortality in patients on maintenance hemodialysis, bioimpedance-derived sarcopenia was not (Item S4a).[3] In another study, subjectively assessed muscle atrophy was associated with mortality more often in women, who also exhibited poor nutritional status (Item S4b). In our study, differences in predialysis VO were present only in absolute terms. Other studies, although not prominently stressing these findings, also indicate larger absolute (Item S4c-e) and even relative (Item S4f) predialysis VO in men. Although some authors suggested that the threshold for relative VO should be sex specific, evidence supporting this claim is so far lacking.[7] Reasons for predialysis differences may in part originate from physiological differences (less extracellular water, therefore less VO) and in part from varying patient preferences. Differences in body composition between sexes are expected, but whether differences in VO are true remains unclear. In bioimpedance spectroscopy, body composition is modeled using the input variables extra- and intracellular resistance, body mass, and body height.[8,9] In the equations used in the Body Composition Monitor, sex-dependent resistivities, body shape factor, and body density were combined into one empirically derived expression with linear dependence on body mass index.[8] Reference populations to derive this body composition model did not exhibit under- or over-representation of sexes but were based on narrower ranges of body mass index than typical hemodialysis populations (25.2 ± 3.7 kg/m^2 vs 26 ± 5.3 kg/m^2), which could lead to erroneous estimates in patients outside of the initial validation range.[3,8,9] Body shape is largely different between sexes, independent of body mass index. The present study is limited by its relatively small sample size and retrospective, cross-sectional design.

In conclusion, we identified notable sex differences in predialysis fluid status and body composition among patients on maintenance hemodialysis at a single center. For VO, these differences have also been observed but have not been commented on or discussed in previous datasets. Considering that the survival of female patients undergoing hemodialysis is equal to (although in some strata slightly better than) male patients, thresholds of body composition parameters associated with increased mortality may not be equal between sexes if the values themselves are sex dependent.[10] We therefore recommend reanalyzing existing large-scale datasets for sex differences in mortality and bioimpedance-derived measures of body composition.

Sebastian Mussnig, MD, Janosch Niknam, MD, Christoph Matthias, Susanne Widmer, Dilara Gülmez, Simon Krenn, MD, Matthias Lorenz, MD, Charles Chazot, PhD, Peter Wabel, PhD, Daniel Schneditz, PhD, and Manfred Hecking, PhD

Table 1. General Data, Dialysis Therapy Data, and Bioimpedance Data of the Study Population Overall and Stratified by Sex

Characteristic	Missing (n %)	Overall, n = 137	Male, n = 85	Female, n = 52	*P*
Population characteristics					
Age (y)	0 (0%)	63.0 (52.0, 74.0)	60.0 (48.0, 72.0)	65.5 (57.8, 75.3)	0.08[a]
Height (cm)	0 (0%)	170.0 (162.0, 176.0)	174.0 (170.0, 180.0)	160.0 (157.0, 164.3)	<0.01[a]
Body mass index (kg/m^2)	0 (0%)	26.6 (23.2, 31.1)	26.5 (23.3, 30.6)	27.1 (22.4, 33.3)	0.6[a]
Body mass pre-HD (kg)	2 (1.5%)	78.3 (67.1, 89.6)	80.8 (69.6, 94.4)	72.7 (63.3, 86.6)	<0.01[a]
Intradialytic weight loss (kg)	5 (3.6%)	2.4 (1.3, 3.0)	2.5 (1.8, 3.3)	2.0 (1.1, 2.5)	<0.01[a]
Difference to dry weight post-HD (kg)	10 (7.3%)	0.1 (−0.1, 0.8)	0.1 (−0.1, 1.0)	0.1 (0.0, 0.7)	0.9[a]
Interdialytic weight gain from last session (kg)	4 (2.9%)	2.3 (1.1, 3.2)	2.5 (1.6, 3.3)	1.8 (0.7, 2.5)	<0.01[a]
Interdialytic weight gain to next session (kg)	6 (4.4%)	2.3 (1.0, 3.1)	2.5 (1.4, 3.3)	1.8 (0.5, 2.8)	0.01[a]
Dialysis vintage (mo)	3 (2.2%)	27.8 (12.6, 56.8)	28.9 (12.1, 52.7)	27.2 (14.8, 61.9)	0.8[a]
Ultrafiltration volume (L)	4 (2.9%)	2.5 (1.7, 3.1)	2.8 (1.9, 3.5)	2.3 (1.5, 2.7)	<0.01[a]
Dialysis therapy duration (min)	43 (31%)	228.5 (207.3, 234.0)	229.0 (218.0, 234.0)	212.0 (181.3, 234.0)	0.03[a]
Systolic BP pre-HD (mm Hg)	3 (2.2%)	144.5 (131.3, 158.0)	143.0 (131.0, 158.0)	146.0 (135.3, 157.0)	0.8[a]
Diastolic BP pre-HD (mm Hg)	3 (2.2%)	73.5 (65.0, 82.0)	74.5 (67.0, 83.3)	71.5 (62.3, 81.0)	0.12[a]
Systolic BP post-HD (mm Hg)	4 (2.9%)	140.0 (123.0, 156.0)	138.0 (120.0, 157.5)	144.0 (126.5, 153.8)	0.7[a]
Diastolic BP post-HD (mm Hg)	4 (2.9%)	72.0 (63.0, 82.0)	74.0 (64.0, 86.5)	70.0 (62.0, 77.0)	0.02[a]
Intradialytic hypotension, (n, %)	7 (5.1%)	13.0 (10.0%)	7.0 (8.8%)	6.0 (12.0%)	0.8[b]
Venous hemoglobin pre-HD (g/dL)	3 (2.2%)	11.4 (10.7, 12.2)	11.7 (10.8, 12.3)	11.2 (10.6, 12.0)	0.09[a]
Previous albumin (g/dL)	2 (1.5%)	3.4 (3.2, 3.7)	3.4 (3.2, 3.7)	3.4 (3.2, 3.7)	0.7[a]
Previous total protein (g/dL)	2 (1.5%)	6.9 (6.5, 7.2)	7.0 (6.6, 7.2)	6.9 (6.4, 7.2)	0.2[a]
Bioimpedance spectroscopy characteristics					
Extracellular resistance (Ohm)	0 (0%)	530.2 (457.9, 590.6)	518.5 (446.4, 564.1)	554.4 (494.6, 620.6)	0.01[a]
Intracellular resistance (Ohm)	0 (0%)	1,596.7 (1,337.0, 1,959.3)	1,501.7 (1,247.7, 1,838.5)	1,844.2 (1,406.1, 2,174.0)	<0.01[a]
Resistance at infinite frequency (Ohm)	0 (0%)	400.8 (342.3, 445.6)	386.1 (327.4, 425.5)	427.4 (371.0, 476.4)	<0.01[a]
Capacitance (nF)	0 (0%)	1.2 (0.9, 1.7)	1.4 (1.0, 1.8)	1.0 (0.8, 1.3)	<0.01[a]
Time delay (ns)	0 (0%)	0.2 (−1.3, 3.1)	0.3 (−1.4, 3.1)	0.2 (−1.3, 3.3)	0.7[a]
α (radian)	0 (0%)	0.6 (0.6, 0.7)	0.7 (0.6, 0.7)	0.6 (0.6, 0.7)	0.04[a]
Extracellular water (L)	0 (0%)	18.5 (16.3, 21.3)	19.8 (17.9, 22.7)	16.3 (14.1, 18.3)	<0.01[a]
Intracellular water (L)	0 (0%)	18.4 (15.6, 21.5)	20.7 (17.7, 23.3)	15.6 (13.6, 18.0)	<0.01[a]
Total body water (L)	0 (0%)	36.7 (31.8, 42.6)	40.7 (36.2, 45.6)	31.4 (28.1, 35.8)	<0.01[a]
Volume overload pre-HD (L)	0 (0%)	2.4 (1.4, 3.5)	2.7 (1.5, 4.0)	1.9 (1.0, 3.0)	0.03[a]
Volume overload pre-HD <2.5 L	0 (0%)	69.0 (50.4%)	37.0 (43.5%)	32.0 (61.5%)	0.06[b]
Relative volume overload pre-HD (%)	0 (0%)	13.4 (7.9, 18.5)	14.3 (8.2, 19.5)	12.0 (6.0, 17.3)	0.4[a]
Relative volume overload pre-HD <15%	0 (0%)	80.0 (58.4%)	47.0 (55.3%)	33.0 (63.5%)	0.4[b]
Lean tissue index (kg/m^2)	0 (0%)	12.4 (10.5, 14.6)	13.4 (11.2, 15.6)	11.0 (9.5, 13.0)	<0.01[a]
Lean tissue index Δ reference (kg/m^2) Lean tissue index between 15-20 kg/m^2	0 (0%) 0 (0%)	0.0 (−1.9, 1.7) 27.0 (19.7%)	−0.4 (−2.1, 1.7) 23.0 (27.1%)	0.4 (−0.8, 2.1) 4.0 (7.7%)	0.02[a] <0.01[c]
Fat tissue index (kg/m^2)	1 (0.7%)	12.2 (9.6, 17.7)	11.1 (9.1, 16.4)	14.2 (9.9, 22.0)	0.04[a]
Fat tissue index Δ reference (kg/m^2)	1 (0.7%)	6.5 (3.6, 11.3)	6.4 (3.7, 9.3)	7.1 (3.0, 14.6)	0.5[a]
Fat tissue index between 4-15 kg/m^2	1 (0.7%)	83.0 (61.0%)	57.0 (67.9%)	26.0 (50.0%)	0.06[b]

Note: Characteristics are reported as number (%) or median (interquartile range). Albumin and total protein measurements were extracted from the most recent routine laboratory before the bioimpedance measurement.
Abbreviations: BP, blood pressure; HD, hemodialysis.
[a]Two-sample Wilcoxon test.
[b]Chi-square test.
[c]Fisher's exact test.

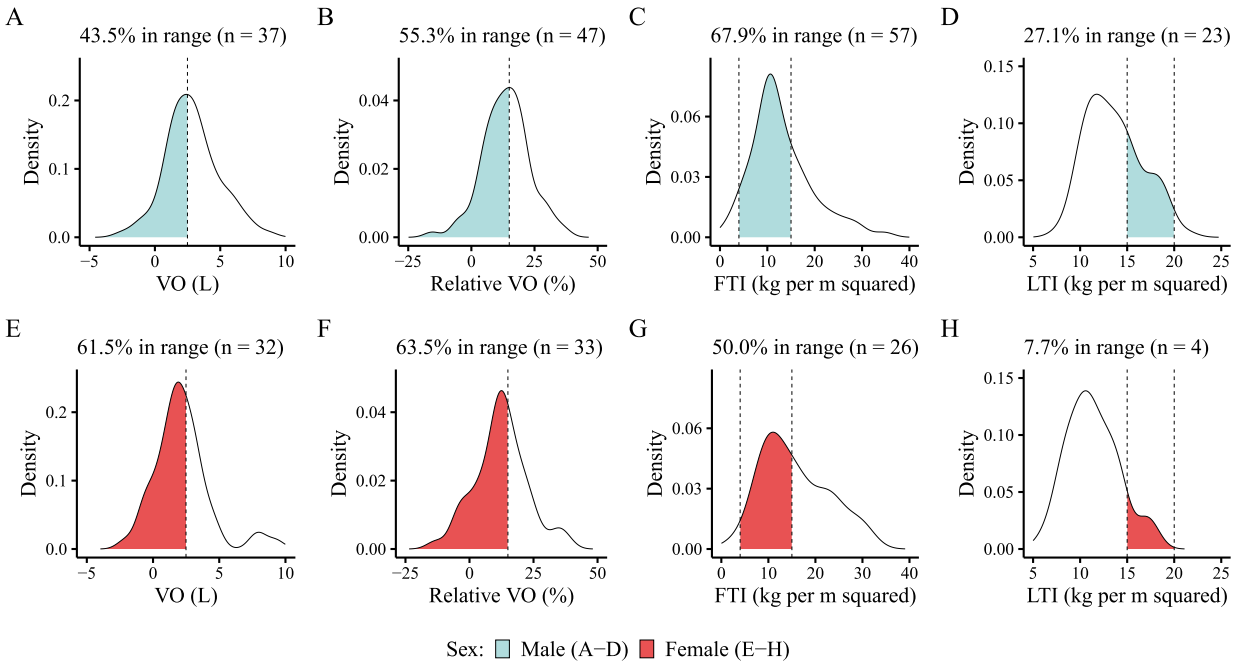

Figure 1. Density plots of fluid and body composition parameters stratified by sex. Dashed lines delimit upper and lower reference thresholds taken from literature.[3,4] Colored areas and annotated percentages show the proportion of patients within these ranges. FTI, fat tissue index; LTI, lean tissue index; VO, volume overload.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Patient flowchart.

Figure S2: Density plots of fluid and body composition parameters stratified by sex.

Figure S3: Equivariant Passing-Bablok regression models and Bland-Altman plots comparing BCM and Cella resistance measurements in supine wrist-to-ankle configurations.

Figure S4: Equivariant Passing-Bablok regression models and Bland-Altman plots comparing BCM and Cella volume measurements in supine wrist-to-ankle configurations.

Figure S5: Equivariant Passing-Bablok regression models and Bland-Altman plots comparing BCM and Cella body composition measurements in supine wrist-to-ankle configurations.

Figure S6: Errors of Cella measurements normalized to BCM wrist-to-ankle.

Figure S7: Bode plots of impedance magnitude and phase for all BIS setups as loess curves.

Item S1: Supplemental Methods.

Item S2: Supplemental Code.

Item S3: Supplemental Results.

Item S4: Supplemental References.

Table S1: Results of all bioimpedance spectroscopy measurements.

ARTICLE INFORMATION

Authors' Affiliations: Department of Epidemiology, Center for Public Health, Medical University of Vienna, Vienna, Austria (SM, JN, CM, SW, DG, SK, MH); Division for Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria (SM, MH); Center for Health & Bioresources, Medical Signal Analysis, Austrian Institute of Technology GmbH, Vienna, Austria (CM, SK); Vienna Dialysis-Center, Vienna, Austria (ML); Department of Nephrology, Clinique Charcot, Sainte Foy Les Lyon, France (CC); Independent Researcher, Rosbach, Germany (PW); Division of Physiology & Pathophysiology, Otto Loewi Research Center, Medical University of Graz, Graz, Austria (DS); Kuratorium for Dialysis and Transplantation, Neu-Isenburg, Germany (MH).

Address for Correspondence: Manfred Hecking, PhD, Department of Epidemiology, Center for Public Health, Medical University of Vienna, Kinderspitalgasse 15, 1st floor, 1090 Vienna, Austria. Email: manfred.hecking@meduniwien.ac.at

Author Contributions: Conceptualization: SM, PW, MH; Methodology: SM; Software: SM; Formal Analysis: SM; Investigation: SM, JN, CM, SW; Resources: MH; Data curation: SM; Visualization: SM; Supervision: MH; Project administration: SM, MH; Funding acquisition: MH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This work was supported by the Vienna Science and Technology (WWTF) Precision Medicine Grant LS20-079.

Financial Disclosure: Dr Chazot and Dr Wabel were previously employees of Fresenius Medical Care, which produces the Body Composition Monitor. Dr Schneditz is a coinventor of patents in the field of blood volume and bioimpedance applications in hemodialysis and is a member of the American Renal Associates research board. Dr Hecking served as a speaker and/or consultant for Astellas Pharma, AstraZeneca, Eli Lilly, Fresenius Medical Care, Janssen-Cilag, Siemens Healthcare, and Vifor and has previously received academic study support from Astellas Pharma, Boehringer Ingelheim, Eli Lilly, Nikkiso, and Siemens Healthcare (not related to the present work). The remaining authors have nothing to declare.

Acknowledgments: The authors wish to thank all medical staff at the Vienna Dialysis-Center and Ole Schecker and Moritz Reuth for additional data acquisition.

Data Sharing: Data will be made available on reasonable request to the corresponding author.

Peer Review: Received March 2, 2024. Evaluated by 1 external peer reviewer, with direct editorial input from the Statistical Editor and the Editor-in-Chief. Accepted in revised form April 30, 2024.

REFERENCES

1. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, et al. Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. *Am J Kidney Dis*. 2005;46(3):489-500.
2. Levin NW, Handelman GJ, Coresh J, Port FK, Kaysen GA. Reverse epidemiology: a confusing, confounding, and inaccurate term. *Semin Dial*. 2007;20(6):586-592.
3. Marcelli D, Usvyat LA, Kotanko P, et al. Body composition and survival in dialysis patients: results from an international cohort study. *Clin J Am Soc Nephrol*. 2015;10(7):1192-1200.
4. Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant*. 2009;24(5):1574-1579.
5. Wieskotten S, Heinke S, Wabel P, et al. Bioimpedance-based identification of malnutrition using fuzzy logic. *Physiol Meas*. 2008;29(5):639-654.
6. Chesnaye NC, Carrero JJ, Hecking M, Jager KJ. Differences in the epidemiology, management and outcomes of kidney disease in men and women. *Nat Rev Nephrol*. 2024;20(1):7-20.
7. Zoccali C, Moissl U, Chazot C, et al. Chronic fluid overload and mortality in ESRD. *J Am Soc Nephrol*. 2017;28(8):2491-2497.
8. Moissl UM, Wabel P, Chamney PW, et al. Body fluid volume determination via body composition spectroscopy in health and disease. *Physiol Meas*. 2006;27(9):921-933.
9. Chamney PW, Wabel P, Moissl UM, et al. A whole-body model to distinguish excess fluid from the hydration of major body tissues. *Am J Clin Nutr*. 2007;85(1):80-99.
10. ERA Registry. ERA Registry Annual Report 2021. Amsterdam UMC, location AMC. Department of Medical Informatics, Amsterdam, the Netherlands, 2023.