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Original article

Are we overfeeding hemodialysis patients with protein? Exploring an alternative method to estimate protein needs

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SUMMARY

Background & aims: Sufficient protein intake is of great importance in hemodialysis (HD) patients, especially for maintaining muscle mass. Daily protein needs are generally estimated using bodyweight (BW), in which individual differences in body composition are not accounted for. As body protein mass is best represented by fat free mass (FFM), there is a rationale to apply FFM instead of BW. The agreement between both estimations is unclear. Therefore, the aim of this study is to compare protein needs based on either FFM or BW in HD patients.
Methods: Protein needs were estimated in 115 HD patients by three different equations; FFM, BW and BW adjusted for low or high BMI. FFM was measured by multi-frequency bioelectrical impedance spectroscopy and considered the reference method. Estimations of FFM x 1.5 g/kg and FFM x 1.9 g/kg were compared with (adjusted)BW x 1.2 and x 1.5, respectively. Differences were assessed with repeated measures ANOVA and Bland–Altman plots.
Results: Mean protein needs estimated by (adjusted)BW were higher compared to those based on FFM, across all BMI categories ($P < 0.01$) and most explicitly in obese patients. In females with BMI >30, protein needs were 69 ± 17.4 g/day higher based on BW and 45 ± 9.3 g/day higher based on BMI adjusted BW, compared to FFM. In males with BMI >30, protein needs were 51 ± 20.4 g/day and 23 ± 20.9 g/day higher compared to FFM, respectively.
Conclusions: Our data show large differences and possible overestimations of protein needs when comparing BW to FFM. We emphasize the importance of more research and discussion on this topic.

1. Introduction

Protein-energy wasting (PEW) is a syndrome that occurs in hemodialysis (HD) patients and has a negative impact on clinical course [1–3]. Multiple mechanism can cause a state of PEW, such as uremic toxicity, inflammation and insufficient protein intake. Ensuring an optimal protein intake is considered an important part of treatment in PEW [1, 2, 4].

In daily practice, dietitians take these factors of PEW into account and subsequently calculate patients' protein needs based on (ideal) bodyweight (BW) which is in accordance with several guidelines [4–7]. In previous studies, a mean protein intake of at least 1.0–1.2 g/kg/day showed a neutral or positive nitrogen

Abbreviations: BIS, bioelectrical impedance spectroscopy; BMI, body mass index; BW, bodyweight; CKD, chronic kidney disease; CT, computed tomography; DXA, dual-Energy X-ray Absorptiometry; FFM, fat free mass; HD, hemodialysis; KDOQI, Kidney disease Quality Initiative; PEW, Protein-energy wasting; SGA, Subjective Global Assessment.

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balance [8–10]. In case of severe PEW, amounts up to 1.5 g/kg/day are also considered (11). In the Netherlands often actual BW is used instead of ideal BW and in previous studies is suggested to adjust BW in under- and overweight patients, using body mass index (BMI) [11,12]. This is based on a study investigating protein needs in ICU patients, in which protein mass, thus fat free mass (FFM), was measured precisely with in vivo neutron activation analysis [13]. In this population, 1.5 g of protein/kg FFM corresponded with 1.2 g of protein/kg BW and 1.9 g of protein/kg FFM with 1.5 g of protein/kg BW. In subjects with a healthy weight, this calculation was accurate, though in patients with under- and overweight this appeared incorrect. Protein requirements in underweight patients are often underestimated, because the body contains relatively more protein per kg BW. In overweight patients the opposite occurs, and consequently protein needs are overestimated when calculated with their current BW. Therefore, arbitrarily in practice, in patients with a BMI below 20, BW is adjusted to BMI = 20 and in patients with a BMI above 27.5, BW is adjusted to BMI = 27.5.

Considering body protein mass is most represented in FFM, why is BW still used when calculating protein needs? This is a topic of discussion in the Netherlands. There is a good rationale to apply FFM instead of BW, because BW doesn't provide information on body composition and individual differences can be expected. A Dutch study investigated these methods in hospital in- and out-patients, and great under- and overestimation in protein needs was seen when using BW, especially in under- and overweight patients [14]. In our clinical practice we noticed these same differences between HD patients. This is of great interest, since insufficient protein intake could contribute to developing PEW [15,16] and excessive protein intake can induce hyperphosphatemia, contributes to metabolic acidosis and in the long-term vascular calcifications [5,17].

It is of great interest to investigate which differences are seen when calculating protein needs based on FFM versus BW. Therefore, the aim of this study is to compare protein needs based on either FFM or BW in HD patients.

2. Materials and methods

2.1. Study design and population

In this prospective study, measurements of body composition were performed between June 2009 and May 2019 as part of regular care. Data of these measurements were included in this study. Patients on maintenance HD, with a conventional or nocturnal schedule, were included. Three dieticians were trained to perform nutritional assessment and regularly performed nutritional assessment in all patients. All patients filled out a written informed consent. This study is in accordance with the Declaration of Helsinki and has been approved by the Medical Ethics Committee (METc).

2.2. Body composition and anthropometric measurements

Body composition was assessed with multi-frequency bioelectrical impedance spectroscopy (BIS), using a Body Composition Monitor (Fresenius Medical Care, Bad Homburg, Germany). Measurements were mostly performed about 30 min after HD treatment, with the intention to measure the most optimal stability in a patient's body fluid compartments. More details regarding body composition and anthropometric measurements were previously described [18].

2.3. Estimation of protein needs

Protein needs were estimated with data on FFM and BW and in this study the estimations of protein needs based on FFM were chosen as reference method. The following equations were used:

- FFM in kg x 1.5 g/kg BW per day compared with BW x 1.2 g/kg/day, as well as BMI adjusted BW (adjustments were made when BMI was below 20 kg/m^2 or above 27.5 kg/m^2).
- FFM in kg x 1.9 g/kg BW per day compared with BW x 1.5 g/kg/day, as well as BMI adjusted BW as previous described.

2.4. Statistical analysis

Patient characteristics were reported as means with standard deviations, medians with interquartile ranges or proportions when appropriate. A consensus was reached by the research group, that an estimation of protein needs within ±10% of the reference method was considered accurate. Below 90% was considered underpredicted, above 110% as overpredicted. Independent samples t-tests were used to determine differences between males and females in subject characteristics and protein needs. Repeated measures ANOVA was used to assess differences in protein needs between males and females and between different BMI groups. Pairwise comparisons of the means were analysed with post hoc Bonferroni test. Bland–Altman plots were created with scatterplots

Table 1
Baseline characteristics (n = 115).

Characteristics	Total group (n = 115)	Males (n = 73)	Females (n = 42)
Sex, male	–	73 [63.5%]	42 [36.5%]
Age (yr)[a]	54.5 ± 15.2	53.7 ± 15.2	55.7 ± 14.7
Mobility			
Mobility in- and outside the house	113 [98.3%]	73 [100%]	40 [95.2%]
Mobility only inside the house	2 [1.7%]	0 [0%]	2 [4.8%]
Dialysis frequency (times/week)[a]	3.0 ± 0.43	3.0 ± 0.44	2.9 ± 0.40
Dialyses (hours per dialysis)[b]	4.0 [4.0–8.0]	4.0 [4.0–8.0]	4.0 [4.0–7.0]
Bodyweight (kg)[a]	76.9 ± 18.2	80.5 ± 17.5	71 ± 17.9
Body mass index (BMI, kg/m^2)[a]	26.1 ± 5.5	25.8 ± 5.2	26.6 ± 6.1
BMI categories			
Underweight (BMI<18.5)	3 [2.6%]	1 [1.4%]	2 [4.8%]
Normal weight (BMI≥18.5–25)	54 [47.0%]	36 [49.3%]	18 [42.9]
Overweight (BMI≥25–30)	35 [30.4%]	24 [32.9%]	11 [26.2%]
Obese (BMI>30)	23 [20.0%]	12 [16.4%]	11 [26.2%]
Fat free mass (kg/m^2) with BIS[a]	41.8 ± 11.8	47.6 ± 9.3	31.8 ± 8.5

[a] Mean ± SD.
[b] median [interquartile range].

of the differences between methods against the mean between methods. The limits of agreement were established as two standard deviations above and below the mean difference. Statistical analysis were performed using SPSS statistics, version 26.0 (SPSS, Chicago, IL, USA). Statistical significance was considered at the level of $P \leq 0.05$.

3. Results

3.1. Baseline characteristics

Table 1 shows baseline characteristics of the study population. A total of 115 HD patients were included in this study, with 64% males (n = 73). The mean age of the total group was 54.5 ± 15.2 years. Mean BW was of 80.5 ± 17.5 kg and a BMI of 25.8 ± 5.2 kg/m^2 in males and mean BW was 70.8 ± 17.9 kg and a BMI of 26.6 ± 6.1 kg/m^2 in females. Mean FFM was 47.6 ± 9.3 kg in males and 31.8 ± 8.5 kg in females ($P < 0.001$).

3.2. Estimations of protein needs by sex

Table 2 shows the estimates of protein needs of the total group by sex. Mean protein needs estimated with BW and BMI adjusted BW all showed higher protein needs in g/day, compared with FFM. In males, comparing FFM x 1.5 g/kg with BW and BMI adjusted BW, mean protein needs were 26 ± 22 g/day and 21 ± 18 g/day higher. In females, higher protein needs were found of 37 ± 26 g/day with BW and 31 ± 16 g/day with BMI adjusted BW. Using FFM x 1.9 g/kg, similar results were found, as shown in Table 2. FFM x 1.5 g/kg and FFM x 1.9 g/kg, compared with both equations in either sex, showed overpredictions of 80% up to 100%.

3.3. Estimations of protein needs by sex and BMI

Figure 1A,B shows the differences in protein needs (g) of FFM x 1.5 g/kg and FFM x 1.9 g/kg compared with BW and BMI adjusted BW, by sex and across BMI groups. In both FFM equations, comparisons with BW and BMI adjusted BW, the difference in protein needs rises with BMI. In males and females, protein needs calculated by BW and BMI adjusted BW were significantly higher compared to FFM, across all BMI categories ($P < 0.01$). In overweight (BMI 25 to 30) and obese (BMI >30) males and females, a large significant difference was found ($P < 0.01$): in overweight males mean protein needs were found to be 30 ± 15.6 g/day higher calculated with BW and 29 ± 15.4 g/day higher when using BMI adjusted BW, in obese males higher protein needs were found of 51 ± 20.4 g/day and 23 ± 20.8 g/day, respectively. In overweight and obese females, mean protein needs were 37 ± 15.5 g/day higher with BW and 35 ± 13.5 g/day higher in BMI adjusted BW, and mean protein needs of 69 ± 17.4 g/day and 45 ± 9.3 g/day in obese females, respectively. Comparisons with FFM x 1.9 g/kg showed corresponding P-values and differences in mean protein needs.

3.4. Bland–Altman analysis

Figure 2A–D shows Bland–Altman plots of mean protein needs and differences in protein needs between BW, BMI adjusted BW and FFM, by sex. In males, FFM x 1.5 g/kg compared to BW showed a mean difference of 25.2 with limits of agreements (LOAs) of −17.3 to 67.7. In the comparison with BMI adjusted BW the mean difference was 20.5 with LOAs of −14.3 to 55.2. In females, FFM x 1.5 g/kg with BW a mean difference was found of 37.2 with LOAs of −12.8 to 87.2. Compared with BMI adjusted BW, a mean difference was found of 31.0 with LOAs of 0.8–62.8.

Table 2
Equations to estimate protein needs in 115 hemodialysis patients, by sex. The reference method on fat free mass (FFM) versus bodyweight (BW) or BMI adjusted BW.

Protein equations	Protein needs (g)±SD	Mean difference± SD (g)	Under-predictions[a]	Accurate predictions[a]	Over-predictions[a]	Limits of Agreement, Bland- Altman	Protein needs (g), mean ± SD	Mean difference± SD (g)	Under-predictions[a]	Accurate predictions[a]	Over-predictions[a]	Limits of Agree-ment, Bland- Altman
	Males (n = 73)						Females (n = 43)					
FFM in kg x 1.5 g/kg (reference)	71 ± 14	–	–	–	–	–	48 ± 13	–	–	–	–	–
BW in kg x 1.2 g/kg	97 ± 21	26 ± 22	1.4%	19.2%	80%	−17.3, 67.7	85 ± 21	37 ± 26	0.0%	0.0%	100%	−12.8, 87.2
BMI adjusted BW in kg, x 1.2 g/kg[b]	92 ± 14	21 ± 18	1.4%	19.2%	80%	−14.3, 55.2	79 ± 11	31 ± 16	0.0%	0.0%	100%	−0.8, 62.8
FFM in kg x 1.9 g/kg (reference)	90 ± 18	–	–	–	–	–	60 ± 16	–	–	–	–	–
BW in kg x 1.5 g/kg	121 ± 26	31 ± 27	1.4%	19.2%	80%	−22.9, 83.6	106 ± 27	46 ± 32	0.0%	0.0%	100%	−17.0, 108.5
BMI adjusted BW in kg, x 1.5 g//kg[b]	115 ± 17	25 ± 22	1.4%	17.8%	81%	−19.4, 68.1	98 ± 14	38 ± 20	0.0%	0.0%	100%	−2.1, 77.9

[a] Under-, accurate or overpredictions, the total of patients predicted within 10% of the mean, estimated reference value.
[b] Adjusted for BMI <20 or BMI >27.5 kg/m^2.

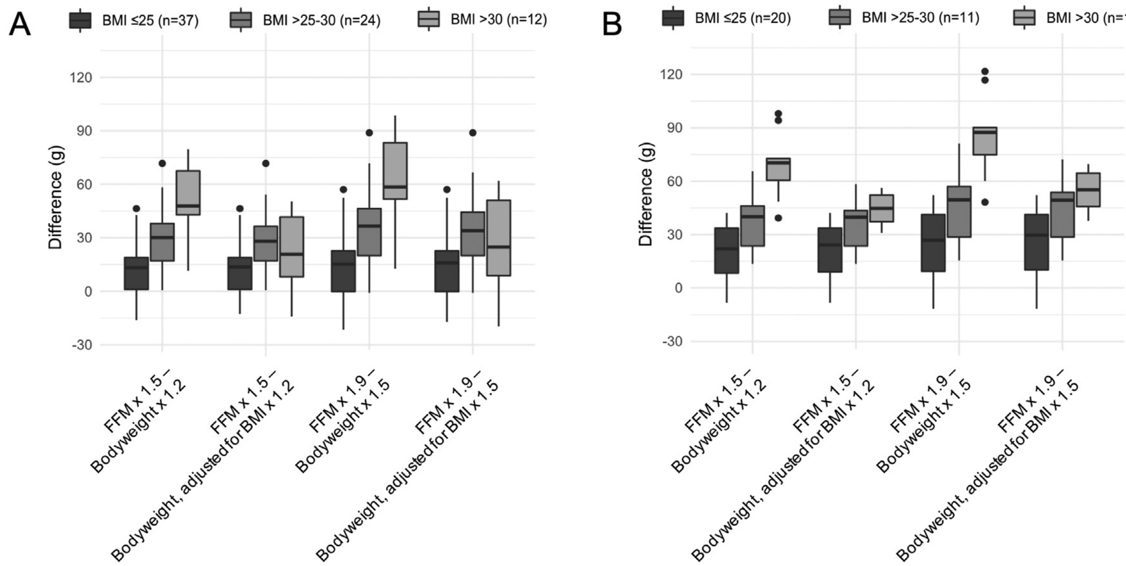

Fig. 1. Differences in protein needs (g) of FFM x 1.5 g/kg versus bodyweight (BW) and BMI adjusted BW x 1.2 g/kg and FFM x 1.9 g/kg versus BW and BMI adjusted BW x 1.5 g/kg by BMI group in **(A)** males and **(B)** females.

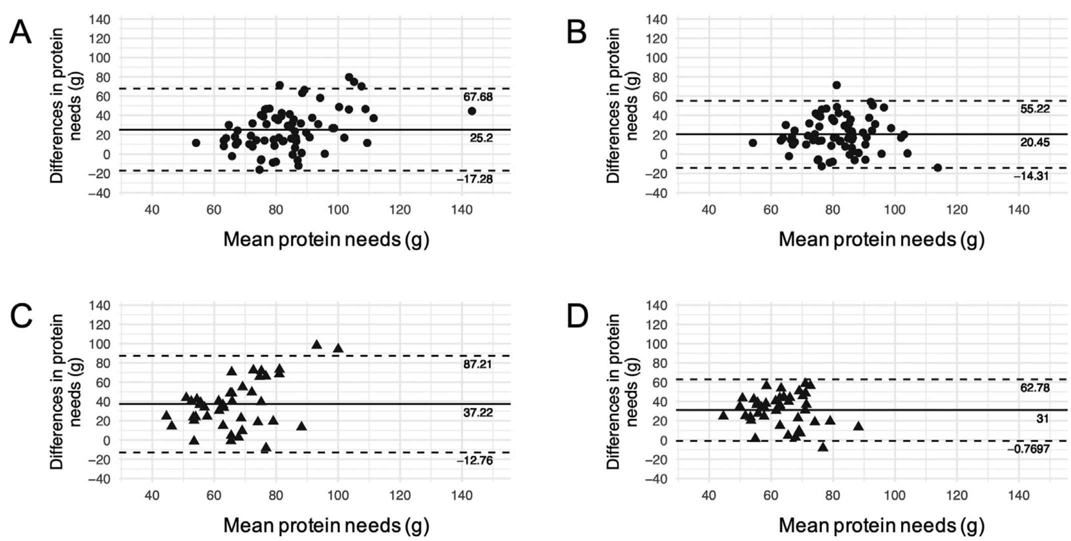

Fig. 2. Bland–Altman plots of protein needs. (**A**) FFM x 1.5 g/kg versus bodyweight (BW) x 1.2 g/kg in males. (**B**) FFM x 1.5 g/kg versus BMI adjusted BW x 1.2 g/kg in males. (**C**) FFM x 1.5 g/kg versus BW x 1.2 g/kg in females. (**D**) FFM x 1.5 g/kg versus BMI adjusted BW x 1.2 g/kg in females.

4. Discussion

This study is discussing the topic on protein estimations by comparing estimations of protein needs based on FFM with estimations based on BW in HD patients. Our results show large differences between these two methods. Exploring different BMI groups, we found enormous overestimations of protein needs, especially in obese patients and more so in females, when considering FFM as reference method.

Our data show large differences in FFM between males and females (males 47.6 kg and females 31.8 kg, $P < 0.001$) and therefore differences in protein needs based on FFM among all BMI groups ($P < 0.01$). These differences in FFM are not unexpected; large differences in FFM between individuals exist, due to biologic factors, such as sex and age, and environmental influences such as daily physical activity [19,20]. However, in most practices dietitians do not measure body composition with e.g. BIS, but often only use BW, BMI or maybe a screening tool to diagnose PEW, such Subjective Global Assessment (SGA). In previous studies a high BMI is associated with better survival in HD patients [21,22] and SGA is assessed as a valid tool to measure a patients' nutritional status [23,24], but BMI or SGA do not distinguish FFM or provide any insight into differences in body composition. Therefore, certainly combined with higher values of BW and BMI, a patient could incorrectly be diagnosed with a good nutritional status whilst having a low FFM. FFM seems to be a more important factor for survival [21,25] and is considered as one of the most meaningful criteria for diagnosing PEW [26]. It seems of great importance that dietitians should perform more nutritional assessments in order to avoid this issue and to gain a complete representation of all important components that are part of protein-energy wasting in HD patients.

It is however, challenging to measure FFM in a reliable and reproducible way. Ideally, FFM is established with an indirect method such as, Dual-Energy X-ray Absorptiometry (DXA) or a computed tomography (CT) scan [27–29] instead of a double indirect method, such as BIS. Unfortunately, these methods are, besides expensive and time-consuming, not available for nutritional assessment. An easier, more convenient method to estimate FFM is by BIS and previous literature shows a good agreement among DXA and bio-electrical impedance techniques [30–33]. In a chronic kidney disease (CKD) population, BIS is considered appropriate, because it can discriminate intra- and extracellular body fluids adequately and is found to give a complementary insight in nutritional status [30,34–39]. BIS is relatively cheap, easy to obtain by a dialysis center and even though BIS is an indirect method for measuring FFM, it still seems more appropriate than using BW and thereby not taking FFM into account at all.

In conclusion, the main goal of this paper is to discuss and create awareness on discrepancies between estimations of protein needs based on FFM and BW. This is a current topic of discussion in the Netherlands, since concerns arise around the use of BW to calculate protein needs. Evidence on this topic is scarce and there are several arguments in favor to use FFM instead of BW. Therefore, it is suggested to use measured FFM as basis for protein needs in order to avoid protein overfeeding in this vulnerable patient group, as well as avoid protein underfeeding as muscle wasting is an ongoing threat. This study shows large differences when using FFM, and when considering FFM as preferable choice, we might be overfeeding patients with protein. Although, there are challenges regarding measuring FFM accurately, we recommend to address this issue more and investigate this topic in further research.

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Statement of Authorship

Manouk Dam: Conceptualization, Methodology, Investigation, Formal analysis, Writing- Original Draft. **Eva Anne Hartman:** Investigation, Formal analysis, Writing- Original Draft. **Hinke Kruizenga:** Conceptualization, Methodology, Writing- Reviewing and Editing. **Brigit C. van Jaarsveld:** Methodology, Writing-Reviewing and Editing. **Peter J.M. Weijs:** Conceptualization, Methodology, Writing- Reviewing and Editing, Supervision.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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