Differences in the prevalence of sarcopenia in peritoneal dialysis patients using hand grip strength and appendicular lean mass: depends upon guideline definitions

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Abstract

Background

Peritoneal dialysis (PD) patients with sarcopenia have increased risk of mortality. There is consensus that sarcopenia should combine assessments of muscle function and mass. We wished to determine the effect of using different operational definitions in PD patients.

Methods

Hand grip strength (HGS) and segmental bioimpedance derived appendicular lean mass (ALM) were measured and the prevalence of sarcopenia determined using the Foundation for the National Institutes of Health Sarcopenia Project (FNIH), European Working Group on Sarcopenia Older Persons (EWGSOP), and Asian Working Group on Sarcopenia (AWGS) definitions.

Results

We studied 155 PD patients, 95 men (61.3%), mean age 63.0 ±14.9 years, 37.4% diabetic, treated by PD 9 (3-20) months with a HGS of 22.5 (15.5-30.2) kg, weight 73.6 ±16.6 kg, % body fat 31.4 ±4.2, and ALM index 7.52 ±1.40 kg/m^2. More patients were defined with muscle weakness using the EWGSOP compared to the FNIH criteria (X2=6.8, p=0.009), whereas fewer patients met the EWGSOP criteria for muscle wasting compared to FNIH body mass index adjustment (X2=7.7, p=0.006). However, when combining both criteria, there was no difference in the prevalence of sarcopenia between the different recommended definitions (11-15.5%).

Conclusion

We report a much lower prevalence of sarcopenia compared to studies in haemodialysis patients. Although there may be an element of patient selection bias, PD patients are not subject to changes in hydration and electrolytes with haemodialysis, which can affect HGS and muscle mass measurements. Using HGS and segmental bioimpedance we found similar prevalence of sarcopenia using EWGSOP, FNIH, AWGS definitions.

Introduction

Loss of muscle mass, often referred to as sarcopenia, is associated with an increased risk of mortality in the general population [1]. Patients with chronic kidney disease are at increased risk of muscle loss due to multiple factors, including dietary restrictions, metabolic acidosis, inflammation, urinary protein losses and reduced physical activity [2-4]. Additionally, peritoneal dialysis (PD) patients lose protein in the spent dialysate [5]. Sarcopenia in PD patients has been reported to be an independent risk factor for mortality [6].

However, muscle mass declines as part of the normal physiologic process of aging, with estimates of losses between 1.0-1.5%, starting after the age of thirty [1]. To differentiate age-associated loss of muscle strength that is not caused by neurologic or muscular disorders, termed dynapenoa, from pathological loss of muscle mass, classifications of sarcopenia now include a measure of muscle function in addition to demonstrating muscle loss, as the rate

of decline in muscle strength is greater than the rate of loss of muscle mass strength, so that muscle strength can diminish, even while muscle mass is maintained or even increased [7].

Previous reports in PD patients have used a variety of measures to estimate muscle mass, with marked differences in the reported prevalence depending on how muscle mass was estimated [8], with increased prevalence when using creatinine kinetics to estimate muscle mass [9]. However, even when using dual energy absorption spectrometry or bioimpedance to measure muscle mass [10,11], there have been marked variations in the reported prevalence of sarcopenia ranging from 11-31% [12,13]. We therefore decided to review the prevalence of sarcopenia in our prevalent cohort of PD patients and comparing the prevalence using current guideline recommendations from Europe, North America and Asia [14-17].

Methods

We retrospectively assessed the prevalence of sarcopenia in adult PD patients who had attended the outpatient clinic of a university hospital for routine assessment of peritoneal membrane testing [18]. Peritoneal transport was calculated as the four hour peritoneal dialysate effluent creatinine to serum ratio, weekly urea clearance (Kt/Vurea) and dietary protein nitrogen appearance calculated by standard methods from 24-hour urine and peritoneal dialysate effluent samples [18]. No patient had been treated for PD peritonitis or had an acute hospital admission within the preceding 3 months. Patients with chronic

infections, systemic inflammatory diseases and those receiving chemotherapy were excluded from study. Relevant medical history and medications were obtained from hospital computerised records. Hand grip strength (HGS) was measured using the grip-D strength dynamometer (Takei Scientific Instruments Co, Nigata, Japan). Patients were instructed and shown how to use the strength gauge, and measurements were made according to the manufacturer's recommendations with patients asked to make their maximal voluntary exertion. Three measurements were made with the dominant (stronger) arm, and the maximal value recorded.

Multifrequency bioelectrical impedance assessments (MFBIA) were made with an 8 electrode multi-frequency segmental bioimpedance device (InBody 720, Seoul, South Korea) using a standardised protocol, after the patient had passed urine and drained out peritoneal dialysate [19,20]. The bioimpedance machine was regularly serviced and calibrated. Blood tests were taken concurrently and analysed by standard methods for urea, creatinine, albumin, haemoglobin, C-reactive protein (CRP) and N-terminal probrain natriuretic peptide (NTproBNP) [20,21].

Patient co-morbidity was assessed using the Davies-Stoke co-morbidity scoring system [22]. Sarcopenia was defined according to the Foundation for the National Institutes of Health Sarcopenia Project (FNIH) cut off weakness with a HGS of < 26 kg for men and < 16 kg for women [14], and then appendicular muscle mass of <19.75 kg for men or < 15.02 kg for women, or a ratio of appendicular lean mass to body mass index (BMI) < 0.789 for men and < 0.512 for

women [15]; the European Working Group on Sarcopenia in Older People (EWGSOP) muscle weakness HGS cut off of < 30 kg for men, < 20 kg for women coupled with an appendicular lean mass index (ALMI) of < 7.23 kg/m^2 for men and < 5.67 kg/m^2 for women [16], and the Consensus Report of the Asian Working Group on Sarcopenia (AWGS) with a HGS cut off of < 26 kg for men and < 18 for women, and an ALMI of < 7.0 kg/m^2 for me and < 5.7 kg/m^2 for women [17]. We calculated prevalence rates of sarcopenia for all patients according to the different clinical guideline recommendations.

Our retrospective audit complied with the UK National Health Service (NHS) guidelines for clinical audit and service development with all patient data anonymised and complied with UK National Institute for Clinical Excellence (NICE) best practices, www.nice.org.uk/media/796/23/bestpracticeclinicalaudit.pdf.

Statistical analysis

Data is presented as mean ± standard deviation, median (interquartile range), or as percentage. Standard statistical tests were used to analyse data, (D'Agostino & Pearson normality test, t test, Mann Whitney U test, Chi square test) with appropriate corrections made for multiple testing, where appropriate. Univariate correlation was by Pearson or Spearman analysis, depending upon whether variables were normally distributed. Statistical analysis used Prism 7.0 (Graph Pad, San Diego, USA) and Statistical Package for Social Science version 24.0 (IBM Corporation, Armonk, New York, USA). Statistical significance was taken as $p<0.05$.

Results

One hundred and fifty-five patients had measurements of HGS, MFBIA body composition and peritoneal membrane assessment (table 1). There was a positive correlation between HGS in the dominant arm and appendicular lean mass in that dominant arm (figure 1), r^2=0.39, p<0.001 for all patients. We classified patients as having muscle weakness according to the cut-off definitions for HGS, reduced muscle mass, and then sarcopenia based on the combination of both muscle weakness and muscle loss (figure 2). More patients were defined as having muscle weakness using the EWGSOP compared to the FNIH criteria (X2=6.8, p=0.009), whereas fewer patients met the EWGSOP cut-off criteria for muscle wasting compared to the FNIH criteria using the body mass index (BMI) adjustment (X2=7.7, p=0.006). However, when combining both criteria, there was no difference in the prevalence of sarcopenia between the different recommended definitions.

There was no difference in prevalence of HGS weakness between those with and without diabetes (X2=0.01, p=1.0), ethnicity (X2=0.7, p=0.7), or PD modality (X2=1.4, p=0.5). Similarly, there was no difference in prevalence of low appendicular lean mass between those with and without diabetes (X2=0.1, p=0.9), ethnicity (X2=0.7, p=0.7), or PD modality (X2=2.9, p=0.2).

As significantly more patients had muscle weakness (dynapenia) than loss of muscle mass, we compared patients using the EWGSOP criteria. Both male and female PD patients who had reduced HGS were older, and had an increased

ratio of extracellular water (ECW) to total body water (TBW) (table 2). Male patients with dynapenia weighed less, and had less muscle mass, even when indexed for height, and also had lower serum albumin, whereas there were no differences for women (table 2). There were no differences in residual renal function, peritoneal dialysis adequacy or normalised protein nitrogen appearance rate between groups.

We then compared patient groups according to EWGSOP criteria for muscle loss (table 3). HGS was lower for those male patients with reduced muscle mass, but not for female patients. Apart from less muscle mass, patients with reduced muscle weighed less. Female patients with less muscle mass had lower BMI and less body fat, whereas male patients with reduced muscle mass had a greater percentage of body fat (table 3).

Discussion

As patients with sarcopenia have an increased risk for mortality [1], then it is essential to have screening tests to detect sarcopenia. Although there is no universally agreed consensus on defining sarcopenia, working groups have generally combined a functional assessment of muscle strength, typically HGS in combination with a loss of appendicular muscle mass [14-17].

Muscle mass and strength decline as part of the normal aging process. Dynapenia is used to describe age-associated loss of muscle strength that is not caused by neurologic or muscular disorders and generally the rate of decline in muscle strength is greater than the rate of loss in muscle mass [7]. Although

older patients are more likely to develop sarcopenia, clinical guidelines do not specify age cut-offs [14-17]. Previous studies have noted, particularly for haemodialysis patients, that the relationship between muscle strength and mass has been weak [8,16]. However, as muscle contains a relatively high amount of water, then the water content of muscle changes with hydration status, and so measurements of muscle mass differ if measured pre- compared to post-dialysis [24,25]. In addition, haemodialysis patients dialysing with an arterio-venous fistula have increased water content of the arm, which again alters the measurement of arm muscle mass [26,27]. There have been fewer studies in PD patients, but again these have often been confounded by the methods used to estimate muscle mass [28,29]. Using segmental, rather than total body bioimpedance, we were able to measure appendicular muscle mass and also compare HGS with muscle mass in the dominant arm and noted a significant positive association.

As expected, muscle mass and HGS were greater in male patients, and younger patients, and female patients had greater body fat mass. Using the definitions for sarcopenia [14-17], then all three work group definitions showed that muscle weakness was more commonly found than reduced muscle mass, which is in keeping with other reports [12,13]. Significantly more patients had muscle weakness using the EWGSOP compared to the FNIH cut-off. The normal ageing process is associated with not only muscle loss, but also a gain in abdominal fat, and this has led to the concept of sarcopenic obesity [30]. As such, the FNIH proposed scaling muscle mass for BMI, and using their cut off,

then more patients were classified as having reduced muscle mass compared to using the EWGSOP criteria. However, when using their definitions of sarcopenia, combining reduced HGS and muscle mass, then there was no difference in the prevalence of sarcopenia between these different guideline recommendations. Peritoneal dialysis patients are exposed to glucose in the dialysate, and absorption of glucose may potentially lead to weight gain and an increased BMI [31]. This may help to explain the differences in muscle mass adjusted for height compared to BMI, without corresponding differences in muscle strength.

We found no association between either residual renal function, or the amount of urea clearance by peritoneal dialysis, or total urinary and peritoneal clearance and sarcopenia, or either of its composites. Similarly, we did not observe differences in patient co-morbidity between the groups using a scoring system devised for UK PD patients [22]. A previous report suggested an association between muscle weakness and congestive heart failure [28], but we did not find any differences in the cardiac biomarker NTproBNP between groups. Male patients with normal HGS strength were significantly heavier, and had both absolute less muscle mass, and also when indexed for height and BMI. Although there were the same trends for female patients, these did not reach statistically significant difference, similarly there was a trend for weaker patients to have more fat. The ratio of extracellular water to total body water was greater for patients with reduced HGS, which would be in keeping with a reduction in intracellular water and cell mass.

Patients with reduced muscle mass weighed less, and female patients had greater muscle loss and also when adjusted for height. In addition, female patients had increased absolute body fat, and also body fat was indexed for height. Male patients with reduced muscle mass had an increased percentage body fat. HGS was reduced in male patients with muscle loss, but not in female patients. Although muscle energy generation may potentially be impaired in uraemia, so that muscle strength and mass may differ [30], we noted a significant correlation between HGS and appendicular lean mass in the arm. As such the difference observed between genders may simply reflect differences in patient selection for PD, and a smaller number of female patients. Alternatively, as female patients generally have greater body fat, and more fat in their arms, then this may account for the differences observed [32].

Several studies have observed an association between sarcopenia and increased mortality [1,6]. We only report an observational cross-sectional study as the number of patients changing modality in UK centres remains high, predominantly due to the transfers from peritoneal dialysis to transplantation and haemodialysis, which may add confounding to longitudinal studies of peritoneal dialysis patients.

Overall, we report a prevalence of sarcopenia of 11.0-15.5% using the different guideline definitions, which compares to 4-63% reported from a variety of studies, including those from patients with chronic kidney disease not on dialysis, to patients initiating and established on haemodialysis [32]. The

lower prevalence reported in our cohort of PD patients may reflect selection bias in terms of selecting patients for peritoneal dialysis.

However, by studying PD patients without the confounders of changes in hydration status between haemodialysis sessions, and the effect of an arterio-venous fistula on the size of the arm, and also using segmental bioimpedance to measure appendicular lean mass rather than relying on other methods which have been recognised to over-estimate muscle loss [29,30], may account for lower prevalence observed. In addition, compared to previous studies which have reported marked differences between the operational definitions of sarcopenia [8], we found that the prevalence did not differ between guideline definitions.

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Figure 1. Spearman univariate correlation between appendicular lean mass (ALM) in the dominant arm and hand grip strength (HGS) in the dominant arm. r =0.54, p<0.0001.

Figure 2. Percentage of patients with muscle weakness using the Hand grip strength (HGS) cut offs for European Working Group on Sarcopenia in Older People. Sarcopenia (EWGSOP), the Foundation for the National Institutes of Health Sarcopenia Project (FNIH), Consensus Report of the Asian Working Group on Sarcopenia (AWGS), and then percentage of patients with reduced muscle according to FNIH appendicular lean mass (FNIH-ALM), and body mass index (BMI) and then the percentage of patients with sarcopenia meeting the combined criteria. ** p<0.01 vs EWGSOP

Table 1. Peritoneal patient demographics. Values expressed as integer, mean ± standard deviation, median (interquartile range). Continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis (APD).

variable	
Male gender (%)	95 (61.3)
Age years	63.0 ±14.9
Diabetic (%)	58 (37.4)
Ethnicity White/Asian/Black (%)	74 (47.7), 48 (31.0), 33 (21.3)
Systolic blood pressure mmHg	140.0 ±23.2
Diastolic blood pressure mmHg	79.2 ±15.2

Patients prescribed anti-hypertensives (%)	119 (76.8)
Peritoneal dialysis treatment months	9.0 (3-20)
CAPD/APD/APD with day time exchange (%)	43 (27.7), 39 (25.2), 73 (47.1)
4-hour dialysate/serum creatinine	0.73 ±0.12
Weekly urinary Kt/Vurea	0.87 (0.4-1.4)
Weekly peritoneal Kt/Vurea	1.11 (0.4-1.4)
Total weekly Kt/Vurea	2.13 ±0.71
Urinary Creatinine clearance ml/min	4.4 (2.2-7.0)
Weight kg	73.6 ±16.6
Fat free mass kg	50.4 ±11.8
Fat mass kg	23.6 ±11.1
Appendicular mass index kg/m^2	7.52 ±1.40
Hand grip strength kg	22.5 (15.5 – 30.2)
Stoke-Davies co-morbidity grade	1 (0-2)

Table 2. patients divided into those with muscle weakness (dynapenia) according to the European Working Group on Sarcopenia in Older People (EWGSOP) cut off for hand grip strength (HGS). Duration of peritoneal dialysis treatment (PD months), weekly urinary urea clearance (Kt/Vu) and peritoneal clearance (Kt/Vp), and total weekly urea clearance (Kt/Vt), normalised protein nitrogen appearance rate (nPNA), body mass index (BMI), skeletal muscle mass (SMM), skeletal muscle mass index (SMMI), appendicular lean mass (ALM), appendicular lean mass index (ALMI), extracellular water (ECW), total body water (TBW), haemoglobin (Hb), serum albumin (Alb), C reactive protein (CRP), N-terminal probrain natriuretic hormone (BNP). * $p<0.05$, **<0.001 , *** <0.001 vs dynapenic group.

gender	Female	Female	Male	Male
dynapenia	No	yes	No	yes
HGS kg	24.0±2.6***	12.9±3.6	38.4±6.5***	20.9±6.2
Patients	44	17	67	26
Age years	57±12**	67±13	56±15***	68±14
PD months	10 (2-23)	8 (3-13)	5.4 (2.5-16)	10 (3-16)
Weekly Kt/Vu	0.96(0.71-1.68)	0.l95(0.55-1.19)	0.91(0.35-1.39)	0.86(0.37-1.43)
Weekly Kt/Vp	1.24(1.02-1.45)	1.08(0.88-1.42)	1.13(0.73-1.6)	1.06(0.83-1.38)
Weekly Kt/Vt	2.47±0.94	2.05±0.69	2.05±0.91	2.09±0.75
nPNA g/kg/day	0.88±0.24	0.92±0.20	0.87±0.24	0.94±0.20
Weight kg	68.1±8.4	66.4±13.5	83.5±16.6**	73.8±14.4
BMI kg/m^2	26.4±6.2	26.9±5.6	27.8±5.0*	25.6±4.3
SMM kg	22.8±4.9	20.9±3.5	33.3±5.2***	28.4±5.7
SMMI kg/m^2	8.85±1.32	8.40±1.07	11.15±1.27***	9.79±1.38
ALM kg	17.0±4.2	16.0±3.2	26.7±4.2***	22.8±5.2
ALMI kg/m^2	6.56±1.16	6.41±0.94	8.68±0.93**	7.85±1.20
ALM/BMI	0.65±0.13	6.41±0.94	0.96±0.19**	0.90±0.21
Fat mass kg	25.5(11.4-35.0)	26.3(19.8-35.5)	21.0(13.8-29.3)	20.9(11.5-28.4)
Fat Mass Index kg/m^2	9.86±4.9	11.1±4.3	7.63±4.0	7.38+3.8
% fat	38.3(25.1-43.6)	40.2(34.9-45.4)	26.1(17.3-32.3)	29.0(16.5-35.3)
ECW/TBW	0.393±0.006*	0.401±0.014	0.394±0.013**	0.402±0.012
Hg g/L	112.7±18.6	107.7±16.4	113.8±13.9	107.7±15.7
Alb g/L	38.6±4.6	37.3±4.8	38.9±4.5**	36.4±4.4
CRP mg/L	2 (1-6)	4.2 (2-13)	2 (1-5)	5 (2-17)
BNP pg/mL	3400(1505-5184)	2562(998-4465)	4243(1158-16336)	7053(1556-18005)

Table 3. patients divided into those with muscle loss according to the European Working Group on Sarcopenia in Older People (EWGSOP) cut off for muscle loss. Hand grip strength (HGS), duration of peritoneal dialysis treatment (PD months), weekly urinary urea clearance (Kt/Vu) and peritoneal clearance (Kt/Vp)., and total weekly urea clearance (Kt/Vt), normalised protein nitrogen appearance rate (nPNA), body mass index (BMI), skeletal muscle mass (SMM),), skeletal muscle mass index (SMMI), appendicular lean mass (ALM), appendicular lean mass index (ALMI) , extracellular water (ECW), total body water (TBW), haemoglobin (Hb), serum albumin (Alb), C reactive protein (CRP), N-terminal probrain natriuretic hormone (BNP). * p<0.05, **<0.001 , *** <0.001 vs reduced muscle mass group.

gender	Female	Female	Male	Male
Muscle mass	Normal	Reduced	Normal	Reduced
HGS kg	17.4±6.5	16.0±5.4	29.0±10.9*	21.3±7.9
Patients	23	38	39	55
Age years	63±14	64±14	62±15	70±18
PD months	8 (3-17)	11.5 (4-23)	8 (2.8-17)	21 (10-30)
Weekly Kt/Vu	0.96(0.68-1.34)	0.79(0.23-2.03)	0.87(.35-1.43)	0.86(0.4-1.26)
Weekly Kt/Vp	1.08(0.93-1.42)	1.23(1.06-2.13)	1.07(0.83-1.44)	1.11(0.73-1.34)
Weekly Kt/Vt	2.13±0.61	2.58±1.11	2.07±0.69	2.08±0.76
nPNA g/kg/day	0.84±0.20	0.99±0.16	0.90±0.26	0.87±0.21
Weight kg	70.5±14.5***	49.7±6.4	79.4±15.8***	67.2±12.3
BMI kg/m^2	27.7±5.7***	21.4±3.0	26.8±4.6	25.2±5.1
SMM kg	22.8±3.6***	16.5±2.2	31.8±5.8***	22.7±2.5
SMMI kg/m^2	8.91±1.0***	7.07±0.69	10.6±1.33***	8.51±1.08

ALM kg	17.4±3.0***	11.5±2.0	25.1±4.7***	17.6±1.9
ALMI kg/m^2	6.77±0.77***	4.92±0.69	8.46±1.02***	6.56±0.71
ALM/BMI	0.65±0.15*	0.54±0.09	0.95±0.19***	0.72±0.12
Fat mass kg	28.4(21.2-35.8)*	19.0(15.0-20.7)	21.0(12.1-29.0)	20.9(17.7-29.4)
Fat Mass Index kg/m^2	11.22±4.66*	7.74±2.4	7.23±3.75	9.06±4.39
% fat	39.8(32.7-43.9)	35.5(32.1-37.6)	26.9(17.4-32.3)**	32.8(28.8-39.0)
ECW/TBW	0.398±0.013	0.398±0.008	0.398±0.014	0.400±0.012
Hg g/L	109.9±16.3	109.2±23.0	109.1±15.0	116.8±14.9
Alb g/L	37.7±4.8	37.6±4.3	37.4±4.8	37.8±3.8
CRP mg/L	3 (1-10)*	7 (1-29)	4 (1-14)	5 (4-9)
BNP pg/mL	2570(1429-4465)	3215(1883-13167)	4774(1214-18004)	8330(5641-12728)