Differences in prevalence of muscle weakness (sarcopenia) in hemodialysis patients determined by hand grip strength due to variation in guideline definitions of sarcopenia

Background

Muscle weakness is associated with increased mortality, and hemodialysis (HD) are at increased risk of muscle loss. There is no universal agreed definition for muscle weakness, so we wished to determine whether using different cut off criteria recommended by clinical guideline groups altered the prevalence in HD patients.

Methods

We measured hand grip strength (HGS) in HD outpatients comparing HGS with clinical guideline cut offs (European Working Group on Sarcopenia in Older People (EWGSOP), National Institutes of Health Sarcopenia Project (FNIH)) and also used to define muscle wasting (sarcopenia), and age and gender matched normative data.

Results

We studied 459 patients, 61.4% male, 47.3% diabetic. The prevalence of muscle weakness was significantly different when measuring HGS; 84.5% using the EWGSOP cut off, 73.2% with FNIH criteria and 75.2% using North American and 56.6% UK normative data ($p<0.01$). On logistic regression, muscle weakness was associated with age (odds ratio (OR) 1.05, $p<0.001$), weight (OR

0.96, p<0.001), serum albumin (OR 0.89, p=0.007), non-diabetic (OR 0.31, p=0.001). In addition, 66.7% of patients with no-comorbidity were weak, compared to 93.8% with highest co-morbidity score, p<0.001.

Conclusion

There is currently no agreed universal definition for muscle wasting (sarcopenia), but the EWGSOP and FNIH advocate HGS cut offs as part of their definition of sarcopenia. The prevalence of muscle weakness varies according to cut off, and whether age and gender matched normative data is used. In addition, patient characteristics in terms of age and co-morbidity also determine the prevalence of muscle weakness.

Introduction

In economically developed countries life expectancy continues to rise, with increasing numbers of elderly patients now treated by dialysis. Although muscle mass naturally declines after the age of 50, muscle wasting is associated with an increased risk for mortality [1]. Loss of lean body mass is often referred to as sarcopenia, a term derived from the Greek word for loss of flesh [2].

Although there is no universally agreed consensus definition of sarcopenia, it is now defined by both European and North American interest groups by including a functional component [3,4]. Measurement of hand grip strength (HGS) has been shown to be both a reproducible and reliable method of assessing forearm muscle strength, and is established as an indicator of muscle status, particularly among older adults [5]. Several recent studies have reinforced the association between HGS with determinations of nutritional status, measurements of muscle mass, functional capacity and over-all health status. In the last few years several studies have confirmed the value of grip strength as a significant predictor of patient mortality, length of hospital stay, and physical functioning [6].

Patients with chronic kidney disease treated by hemodialysis are at increased risk of losing muscle mass, due to multiple factors, including dietary restrictions, metabolic acidosis, insulin resistance [7], urinary and dialysate protein losses, reduced physical activity, along with fatigue and self-reported depression [8,9]. Reports of studies using HGS measurements in hemodialysis patients have shown that HGS measurements are reliable and reproducible, and not affected by the presence of an arterio-venous fistula or the dialysis session [10-12]. In addition, HGS weakness in hemodialysis patients is associated with increased mortality risk [13].

As there has been recent concordance in defining sarcopenia firstly by a loss of muscle strength measured by HGS by both the European Working Group on Sarcopenia in Older People (EWGSOP) [3] and the North American

Foundation for the National Institutes of Health Sarcopenia Project (FNIH) [4], we wished to determine the prevalence of muscle weakness using these definitions, as well as comparing muscle weakness with age and sex matched controls [14-17].

Methods

We retrospectively analysed the results of HGS using the grip-D strength dynamometer (Takei Scientific Instruments Co, Nigata, Japan) in adult patients with chronic kidney disease attending for outpatient hemodialysis under the care of a university hospital. 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 arm, and the maximal value recorded.

Muscle weakness was defined according the EWGSOP and FNIH sarcopenia cut off definitions (EWGSOP male 32 kg, female 22 kg; FNIH sarcopenia male < 26 kg, female < 16 kg), [3,4] respectively and more than 2 standard deviations (SD) below age and sex matched normative adult values [15,17]. When comparing clinical guideline cut offs, as the dialysis population was from a European center we chose the EWGSOP as the reference clinical guideline. We used the World Health Organisation body mass index (BMI) cut offs (23·0, 27·5, 32·5, and 37·5 kg/m^2) to divide patients into 5 categories [18].

Patient demographics were obtained from hospital computerized health care records. Patient co-morbidity was determined using the Davies-Stoke co-morbidity scoring system, as this has been validated in a UK dialysis population [19]. Patients dialysed using polysulfone dialyzers (Nipro, Osaka, Japan) [20], and Fresenius 4008H, 5008 (Fresenius AG, Bad Homberg, Germany) or BBraun Dialogue+ (BBraun, Melsungen, Germany) dialysis machines, and anticoagulated with tinzaparin, a low molecular weight heparin (Leo Laboratories, Market Harborough, UK) [21].

Serum biochemistry samples were analysed with a standard multi-channel biochemical analyzer (Roche Integra, Roche diagnostics, Lewes, UK), using the bromocresol green method for albumin determination, and hemoglobin samples by the sodium lauryl sulphate-Hb method (XE-2100 Sysmex Corporation, Kobe, Japan) [22], and dialysate biochemistry checked [23]. Dialyzer clearance was calculated on sessional urea clearance (single pool Kt/Vurea), and that estimated by the dialysis machine (on-line Kt/V). Urea appearance rate was calculated as the difference in total body urea pre- and post-dialysis, using total body water pre- and post-dialysis divided by the interdialytic period, and then adjusted to a 70 kg patient. B2 microglobulin was measured using a nephelometric assay [24].

This retrospective audit complied with the UK National Health Service (NHS) guidelines for clinical audit and service development, (UK NHS guidelines for clinical audit and service development, available at http://www.hra.nhs.uk/documents/2013/09/defining-research.pdf, and

http://www.gov.uk/government/publications/health-research-ethics-committees-governancearrangements.

Statistical analysis

Data is presented as mean ± standard deviation, median (interquartile range), or percentage. Standard statistical tests were used to analyse data (D'Agostino and Pearson normality test, kappa test, Wilson agreement, misclassification, t test, Mann Whitney U test, or Chi square test) with appropriate post hoc corrections made for multiple testing (Bonferroni and Benjamini-Hochberg), where appropriate. Binary regression model was developed by including all variables thought to be clinically relevant and then excluding variables which were either not significant or did not improve model fit. Statistical analysis used Prism 6.0 (Graph Pad, San Diego, USA), Analyse-It 4.0 (Analyse-It, Leeds, UK) and SPSS 24 (University Chicago, Chicago, USA). Statistical significance was taken as $p<0.05$.

Results

We retrospectively analysed the results of body composition from 459 adult hemodialysis patients; 282 males (61.4%) male, mean age 66.9 ±15.0 years, 46.6% diabetic, with a median vintage hemodialysis treatment 36.4 (15.2-72.4) months. The major ethnic groups were white 43.4%, south Asian 26.5%, African-Afro-Caribbean 20.3%, East Asian 5.6%, and other ethnic groups 4.2%. Mean HGS was 18.3 ±9.5 kg. Depending on the cut off criteria advised by different

studies, more male patients had muscle weakness using the EWSOP cut off values, and more women had muscle weakness using the EWSOP guidelines compared to the FNIH sarcopenia project or Dodd and Bohannon normative values (Figure 1).

We then compared the prevalence of muscle wasting using the EWGSOP cut off criteria, with those of the FNIH sarcopenia project, Dodd and Bohannon normative values (table 2). There was poor agreement between muscle weakness according to the EWGSOP cut off and those from the FNIH sarcopenia project or Dodd and Bohannon normative values.

As expected male patients had greater HGS than females, and older patients had weaker muscle strength (table 1). Patients with muscle weakness had lower weights, but BMI was only lower in male patients. Pre-dialysis systolic blood pressure was similar between groups, although those patients with reduced HGS had lower pre-dialysis diastolic blood pressures. Haemoglobin and C reactive protein (CRP) were not different, although serum albumin and cholesterol were lower in those with muscle weakness. Dialysis vintage, in terms of months of dialysis treatment and β2 microglobulin were not different, as was dialysis urea clearance (urea reduction ratio) and dialysis machine estimated and calculated sessional Kt/Vurea.

Patients with muscle weakness had greater co-morbidity scores, but apart from previous myocardial infarction, coronary artery stenting and diabetes, other co-morbidities including peripheral vascular disease, stroke, transient ischemic attacks, cirrhosis and malignancy were not different (table

3). Using the EWSOP guidelines for defining sarcopenia, then there were no differences between ethnic groups for women, although fewer African-Afro-Caribbean male patients had muscle weakness (Figure 2).

A logistic regression model for muscle weakness showed that older age, diabetic status, lower weight and serum albumin were all independently associated with muscle weakness (table 4), whereas gender was not a significant factor.

Discussion

Sarcopenia is associated with an increased risk of mortality [1]. To detect muscle loss at an early stage to allow for effective interventions, rapid, low cost screening tests are required for every day clinical practice. Although relying on patient participation requiring a measurement of maximum voluntary muscle strength, HGS has been shown to be a reliable reproducible test to detect muscle weakness, that can be readily performed in the clinic and on the dialysis unit [13,25]. Previous reports have shown that HGS is a robust test of muscle strength which is not affected by patient self-reported distress [26]. Although there is no consensus definition for sarcopenia, speciality interest groups in both North America and Europe recommend measuring HGS in diagnosing sarcopenia [3,4].

We measured HGS in a large multi-ethnic dialysis population attending for outpatient dialysis treatments. Using the EWGSOP cut off, muscle weakness was more commonly found in older patients with lower body weight. Overall co-

morbidity scores were greater in those patients with muscle weakness, and they were more likely to have a medical history of myocardial infarction or coronary artery stenting, which may account for the lower diastolic blood pressure. In addition, diabetic patients were more likely to have muscle weakness, and other studies have reported that diabetic dialysis patients have greater body fat and less muscle mass than non-diabetics [27]. Previous reports have suggested differences in body composition between different ethnic groups [28], and we noted a lower prevalence of muscle weakness for male patients of African-Afro-Caribbean descent. There was no difference in dialysis vintage or β2 microglobulin, a marker of residual renal function [28], between groups of patients divided by gender and muscle weakness. Similarly, urea dialyzer clearance was not different. Indicating that the clearance of small azotaemic solutes, such as urea, or middle molecule clearance of β2 microglobulin or residual renal function may not be associated with reduced muscle function. For male patients, those who were weaker had lower serum urea, albumin, cholesterol and urea generation rate, whereas only albumin and cholesterol were significantly lower in the weaker female patients. This would suggest that these patients probably had lower nutritional intakes, and previous studies have reported an association between muscle weakness and malnourishment in dialysis patients [29], although lower urea generation could also be associated with less physical activity [30], another cause of muscle wasting [7]. In addition, the lower serum albumin could be in keeping with an inflammatory state, although C

reactive protein concentrations did not differ. Previous reports have described a syndrome of muscle wasting and inflammation in dialysis patients [31].

Comparing the EWGSOP cut off with that recommended by the FNIH sarcopenia project group, then the prevalence of muscle wasting was greater using the EWGSOP guidelines [3,4]. In addition, we also used age and gender matched normative data. The prevalence of muscle weakness was lower using UK and North American age and gender matched normative data for males, but there was no difference between EWGSOP and North American age matched data, whereas the prevalence of muscle weakness was much lower using UK age matched normative data [5,13]. As neither the EWGSOP and FNIH sarcopenia cut offs are age adjusted one would expect that they would over estimate muscle weakness when comparing muscle strength with age adjusted normative data. The difference between genders may have been due to the slightly lower age of our female patients.

As muscle strength decreases with age [5,13], on multivariable analysis using the EWGSOP cut off then older age was the strongest factor associated with muscle weakness, followed by lower weight. Diabetic patients and lower serum albumin were also independently associated with muscle weakness.

There is currently no single agreed consensus definition for muscle wasting to differentiate muscle wasting that is associated with the normal aging process from pathological muscle loss, and our study highlights the differences between current guidelines. Similarly, it remains to be established whether the criteria for muscle loss should be disease specific. As although patients with

chronic conditions are generally less physically active, some diseases are more likely to be associated with joint and metabolic bone disease, and so may have additional effects on reducing muscle strength as assessed by HGS.

Taking different cut-offs leads to differences in reported prevalence of muscle wasting, potentially leading to over reporting and conversely under reporting between studies [30,32]. In addition, differences in patient demographics will also have an effect on reported prevalence. As we performed a cross sectional assessment we do not have outcome data to determine an association between muscle weakness and mortality risk. Whether muscle weakness is a primary risk factor for mortality [33], remains to be determined as muscle weakness is also associated with increasing co-morbidity and lower serum albumin.

The authors have no conflict of interest
The data presented in this paper has not been previously published in part or full form

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Figure 1. Percentage of haemodialysis patients with loss of muscle strength measured by hand grip strength according to European Working Group on Sarcopenia in Older People (EWGSOP) and the North American Foundation for the National Institutes of Health Sarcopenia Project (FNIH), and more than 2 standard deviations from sex and age matched normative data, with 1st author name.

$p < 0.05$, ** < 0.01, *** < 0.001 vs EWSOP

Figure 2. Percentage of haemodialysis patients with loss of muscle strength measured by hand grip strength according to ethnicity: White, South Asian and African-Afro-Caribbean, East Asian according to European Working Group on Sarcopenia in Older People (EWGSOP) criteria. $p < 0.05$ vs EWGSOP

Table 1. Cut off values to determine muscle weakness using the European Working Group on Sarcopenia in Older People (EWGSOP). Hand grip strength (HGS), body mass index (BMI), pre-dialysis systolic and diastolic blood pressure (SBP, DBP), haemoglobin (Hb), serum phosphate (Pi), cholesterol (Chol), C reactive protein, glucose (Gluc), β2 microglobulin (β2M), urea reduction ratio (URR), on-line Kt/Vurea, single pool Kt/V (spKt/Vurea), urea appearance rate mmol/day adjusted to 70 kg (nUAR).
* $p<0.5$, ** $p<0.01$, *** $p<0.001$ vs no weakness cohort.

gender	Female		Male	
EWGSOP	normal HGS	reduced HGS	normal HGS	reduced HGS
HGS kg	24.4 ±3.0	11.6 ±4.6***	37.4 ±7.2	18.2 ±6.4***

Age years	52 ±15	68 ±14***	55 ±13	70 ±14***
Weight kg	69.8 ±19.2	65.7 ±19.2***	83.3 ±20.4	71.8 ±14.5***
BMI kg/m^2	26.8 ±8.4	27.0 ±6.9	27.4 ±6.1	25.5 ±4.7**
preSBP mmHg	139 ±19	140 ±31	146 ±18	141 ±26
preDBP mmHg	78 ±15	71 ±17**	80 ±18	70 ±15***
Hb g/L	108.1 ±14.8	108.7 ±13.7	111.9 ±14.1	109.5 ±14.8
Albumin g/L	40.7 ±2.9	37.7 ±4.3***	40.8 ±3.5	38.3 ±4.4***
Urea nitrogen mg/dL	49.9 ±16.5	48.7 ±17.6	59.42 ±12.6	51.0 ± 16.0**
Pi mg/dL	4.8 ±2.1	4.8 ±1.5	5.4 ±1.5	4.8 ±1.5***
Chol mg/dL	173 ± 81	151 ±42*	158 ±42	135 ± 35*
CRP mg/L	3 (1-10)	5 (2-12.5)	5 (2-10)	6 (3-14)
Gluc mg/dL	117 ±40	148 ±58	144 ±68	142 ±56
β2M mg/L	32.2 ±10.0	31.1 ±9.0	29.4 ±8.9	30.3 ±8.6
Vintage months	30.2 (9.8-46.5)	36.4 (15.0-72.0)	29.4 (9.6-42.3)	43.0 (16.8-74.7)
URR %	76.2 ±6.7	76.4 ±9.9	68.7 ±10.8	71.8 ±11.4
OL-Kt/Vurea	1.4 ±0.2	1.4 ±0.2	1.5 ±0.2	1.5 ±0.3
spKt/Vurea	1.67 ±0.29	1.74 ±0.40	1.35 ±0.34	1.51 ±0.38
nUAR	250 ±80	272 ±82	312 ±99	275 ±105*

Table 2. Comparison of European Working Group on Sarcopenia in Older People (EWGSOP) cut off criteria, with muscle weakness cut off advised by North American Foundation for the National Institutes of Health Sarcopenia Project (FNIH), and more than 2 standard deviations from sex and age matched normative data, with 1st author name. Misclassification (Misclass) Sensitivity (Sens), specificity (Spec), Positive predictive value (PPV), negative predictive value (NPV).

	Chi square	kappa	Wilson	Misclass	sens	spec	PPV	NPV
FNIH	17.7 p<0.001	-0.11	0.91	0.56	36.6	46.4	0.16	0.73

Dodd	11.9 p =0.001	-0.09	0.58	0.64	26.3	29.4	0.16	0.57
Bohannon	84.6 p<0.001	-0.28	0.85	0.55	38.4	47.1	0.16	0.75

Table 3. comorbidity – past medical history and co-morbidity scores between patients with and without muscle weakness using the European Working Group on Sarcopenia in Older People (EWGSOP) cut off criteria.

variable	No weakness	Muscle weakness	Chi square
Not Diabetic	22.7	77.3	X2 17.4
Diabetic	7.9	92.1	p <0.001
No myocardial infarction	18.5	81.5	X2 7.4
Myocardial infarction	7.1	92.9	p=0.006
No coronary artery stent	17.2	82.8	X2 5.1
Coronary artery stent	3.9	96.4	p=0.024
Davies co-morbidity score			
0	33.3	66.7	
1	14.8	85.2	X2 23.9
2	6.2	93.8	p <0.001

Table 4. Logistic regression of muscle wasting using the European Working Group on Sarcopenia in Older People (EWGSOP) cut off criteria. Standard error (StE), odds ratio (OR), 95% confidence limits of odds ratio (95% CL). Nagelkerke r^2= 0.33

variable	β	StE β	Wald	OR	95% CL	p
Age yr	0.05	0.01	24.0	1.05	1.03-1.07	<0.001
Weight kg	-0.04	0.01	19.5	0.96	0.95-0.98	<0.001
Albumin g/L	-0.11	0.04	7.3	0.89	0.83-0.97	0.007
Diabetic not	-1.17	0.37	10.3	0.31	0.15-0.69	0.001
Sex male	0.12	0.32	0.13	1.12	0.59-2.12	0.72