Loss of Appendicular muscle mass in haemodialysis patients is associated with increased self-reported depression, anxiety and lower general health scores

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Abstract

Aims

Depressive symptoms are commonly reported by haemodialysis (HD) patients. Previous reports have suggested an association between depression and nutritional status. To investigate this, we measured muscle mass in HD patients screened for depression.

Methods

The Beck Depression Inventory-II (BDI-II), Hospital Anxiety and Depression Scale (HADS) were used to screen for depression, and quality of life assessed by the short form 36 (SF36), and measured appendicular lean mass (ALM) post-dialysis with segmental bioimpedance.

Results

We studied 113 patients, 84 (74.3%) male, mean age 64.9 ±14.9 years, median duration of haemodialysis 27.0 (15.7-61.0) months, body mass index (BMI) post-dialysis 25.2 (22.8-28.6) kg/m^2, ALM index 6.98 (6.22-8.10) kg/m^2. BDI-II 11 (4-17), HADS 10 (5-16.5), and SF36 average 43.3(36.6-48.4). Lower ALM index was associated with greater BDI-II and HADS depression scores (r=0.29, p=0.008; r=0.27, p=0.012) respectively, and higher ALM index associated with improved scores on the SF36 physical functioning and general health subscales (r=0.34, p=0.001; r=0.26, p=0.019), respectively. On logistic regression, lower ALM index was independently associated with high HADS cut off ≥8 (standardised β-0.31, p=0.007). There were no associations with weight, BMI or fat index. Greater extracellular water both pre- and post-dialysis

was associated with reduced SF36 physical functioning (r= -0.24, p=0.011, r=-0.22, p=0.26), respectively.

Conclusion

This is the first report showing an association between ALM index and increased self-reported depression, anxiety and decreased general health. Whether treatment programs designed to improve muscle mass, can lead to reduced levels of depression, and anxiety and improved perceived general health, remains to be determined.

Introduction

Major depressive and mood affective disorders are reported to be more common in patients with chronic diseases. Although haemodialysis is an established treatment for chronic kidney disease, haemodialysis patients have an expected 5-year survival lower than that for some of the more common solid organ cancers [1]. Not only must haemodialysis patients cope with the disruption to life-styles imposed by attending for standard thrice weekly in-centre haemodialysis schedules, they are also required to comply with dietary and fluid restrictions, and a high pill burden. As such reports suggest that depression is common amongst dialysis patients, with prevalence rates varying between 39% based on self-reported screening and 23% based on psychiatric interview [2], with depressed haemodialysis patients having greater mortality [3]. However, depression is more difficult to diagnose because of the overlap of symptoms between depression and those associated with end stage kidney disease [4], with the screening self-reporting questionnaires containing several questions detailing assessments of fatigue [5,6]. Fatigue is a symptom commonly reported by

haemodialysis patients [5]. Patients with chronic kidney disease are more likely to suffer greater muscle loss, termed sarcopenia, due to a combination of multiple factors, including metabolic acidosis, vitamin D deficiency, insulin resistance, anaemia, reduced physical activity, testosterone deficiency in men, protein losses with dialysis, dietary restrictions and depression [7-10]. The European Society for Clinical Nutrition and metabolism (ESPEN) recommends bioelectrical impedance and dual electron absorptiometry (DEXA) scanning to assess muscle mass and body composition [11], and studies in haemodialysis patients have reported equivalence between methods [12].

Previous reports have demonstrated an association between loss of muscle mass, often termed sarcopenia, and depressive symptoms in the general population [13,14]. We therefore wished to determine whether there was an association between loss of muscle mass and self-reported depression and fatigue by comparing measurements of muscle mass with validated patient self-reported questionnaires.

Methods

138 haemodialysis patients attending for outpatient haemodialysis treatments, dialysing under the care of a university hospital who met study entry criteria of being more than 18 years old, spoke English, and were able to provide written informed consent and attending two RFH dialysis units, were screened for depression and anxiety using self-reporting questionnaires: Beck Depression Inventory-II (BDI-II) [6], Short-Form Health Survey (SF-36) [15], and the Hospital Anxiety and Depression Scale (HADS) [16]. Patient demographics and co-morbidity were recorded from

hospital computerised medical and dialysis records, and co-morbidity graded using the Stoke-Davies scale [17].

113 patients had been established on haemodialysis for more 3 months and had corresponding bioimpedance measurements performed in a standardised manner both prior to and then after completion of the mid-week dialysis session using an eight electrode bioimpedance device (InBody 720, Seoul South Korea), as part of established routine clinical care [18,19]. Patients were allowed a recovery period after completion of the dialysis session prior to the post-dialysis bioimpedance measurement. Extracellular water (ECW) was expressed as a percentage of total body water (TBW), and ECW excess defined as difference between ECW measured and that predicted from intracellular water (ICW) as recommended by the ESPEN [11]. Sarcopenia was defined according to the European working group (EWGSOP) (7.25 kg/m^2 for men and 5.67 kg/m^2 for women) [20]. Patients with amputations, and those with pacemakers and other implantable cardiac devices were excluded from study.

Patients were dialysed using polysulphone dialyzers (Nipro, Osaka, Japan) [21], and Fresenius 4008H, 5008 (Fresenius AG, Bad Homberg, Germany) or BBraun Dialogue+ (BBraun, Melsungen, Germany) dialysis machines, using ultrapure dialysis water quality and anticoagulated with tinzaparin, a low molecular weight heparin (Leo Laboratories, Market Harborough, UK) [22].

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 haemoglobin samples by the sodium lauryl sulphate-Hb method (XE-2100 Sysmex Corporation, Kobe, Japan) [23].

Ethics

All patients provided appropriate informed written consent in keeping with the Helsinki agreement, prior to receiving questionnaires. The study received ethical approval from Newcastle and North Tyneside 2 National Research Ethics Committee (ref 13-NE-0087). Patients who expressed suicidal ideation or whose score on any of the references tests gave cause for concern were discussed with a senior clinician in the research team and appropriate action taken.

Statistical analysis

Data normality was checked using the D'Agostino-Pearson, and reported as mean and standard deviation, or median and interquartile range, or percentage and intergroup analysis was by standard methods with correction for repeated tests and for small numbers, where appropriate. After univariate analysis, multivariate logistic step backward analysis was used for determinants of an increased BDI score, and HADS, including variables significant on univariate analysis <0.1, and those thought to be clinically relevant; age, sex, C reactive protein, diabetic status, co-morbidity, ethnicity, months since starting HD, serum albumin, haemoglobin, ECW/TBW, and ALM index. Nonparametric parameters were log transformed. Variables were then excluded in a step backward analysis if not significant, or did not improve model fit, and models were checked for collinearity. Analyses were performed with Graph Pad Prism (Graph Pad Prism V6.0, San Diego, USA) and SPSS 24 (SPSS 24, University Chicago, Illinois, USA). Statistical significance was taken as $p<0.05$.

Results

We studied 113 patients, 84 (74.3%) male, mean age 64.9 ±14.9 years, median duration of haemodialysis 27.0 (15.7-61.0) months. Fifty-eight patients were of white ethnicity (51.3%), followed by 27 (23.9%) African Afro-Caribbeans and 27 (23.9%) Asians. Patient body composition, serum chemistries and self-reported questionnaires scores are set out in table 1.

There were no statistical univariate associations between pre-dialysis weight or body mass index (BMI), haemoglobin, serum chemistries, months of haemodialysis treatment or β2 microglobulin, - a marker of residual renal function, dialysis sessional urea clearance, or Stoke-Davies co-morbidity score and BDI-II, HADS or SF36 self-reported questionnaire scores. There were negative associations between the SF36 physical functioning questionnaire and age (r=-0.22, p=0.02), both pre- and post-dialysis ECW/TBW (r= -0.24, p=0.011, r=-0.22, p=0.26), and ECW excess adjusted for total ECW again pre- and post-dialysis (r=-0.23, p=0.17, and r=-0.21, p=0.03), respectively.

We excluded patients with previous polio and severe limb disability following a stroke, and determined appendicular lean mass (ALM) index in 88 patients (table 2). There was no difference in the prevalence of sarcopenia between races (X2=4.8, p=0.19), or with diabetes, but more male patients had a reduced ALM index (X2=9.5, p=0.02). Reported HADS scores were greater for women. There were no differences for BDI-II or HADS between those with normal and reduced ALMI. There were differences with the SF36 scores for the male patients, for social functioning, general health and overall score (table 2).

We then compared measurements of body composition with the self-reported questionnaire scores. To compare patients, measurements were indexed to height. Although there were no associations with fat mass index, there was a consistent association between estimations of muscle mass; fat free mass, soft lean mass and ALM and SF36 physical functioning (table 3). The greater the ALMI the higher the SF36 scores, but there were negative associations between ALM index and depression scores with the BDI-II and HADS questionnaires.

Logistic regression models were analysed using a cut point score of ≥16 for the BDI-II [5], and ≥8 for the HADS questionnaire [24]. In the BDI-II model, patients with a high score were female and had been treated by haemodialysis for longer, and although loss of ALM (sarcopenia) remained in the model, ALM loss was not independently significant (p=0.06) (Table 4). Whereas in the HADS model, ALM index was independently associated with a lower HADS score, and increasing C reactive protein associated with a high HADS score.

Discussion

Studies of both peritoneal and haemodialysis patients have noted that dialysis patients report a higher level of depressive symptoms compared to age matched controls [2,4]. The standard screening questionnaires used to detect depression include questions related to fatigue. Despite the introduction of erythropoietins and the correction of anaemia, many dialysis patients also report fatigue [5].

We did not find any association between the adequacy of dialysis treatments, or duration of haemodialysis treatments and self-reported depression screening and

health status questionnaire scores, in keeping with previous reports [25,26]. In keeping with previous reports, anxiety scores were greater for women than men, and more men generally reported more physical activity [25,27]. On the other hand, older age and increasing co-morbidity were not associated with greater self-reported depression or worse quality of life. Previous reports have proposed that patient perception of illness and wellbeing have a greater effect than chronological age or co-morbidity [28]. Patients gain fluid weight between haemodialysis sessions, and this excess fluid gain is then removed during the subsequent dialysis session. Whereas we found that increasing ECW, either pre- or post-dialysis was associated with a reduction in physical functioning, we did not find any association between increasing ECW, either pre- or post-dialysis and self-reported depression or anxiety scores.

Previous studies have reported an association between depression and anxiety with nutrition in both the general population [13,14] and dialysis patients [29-31]. However, these earlier studies tended to use serum albumin, as a marker of nutritional status, and lower serum albumin concentrations may reflect inflammatory states, rather than malnutrition. More recently the interaction between inflammation and depression has been queried [32], suggestive of association rather than actual causality. Indeed, we found no univariate association with serum albumin, or cholesterol and the depression, anxiety or general health questionnaires.

We report the first study in which body composition was measured by segmental bioimpedance. As bioimpedance measurements of muscle mass can be affected by overhydration [33], we made measurements after the mid-week haemodialysis session., to minimise this potential confounder. Patients were classified on the basis of reduced

ALM index, and whereas male patients were equally distributed, only a minority of women patients had a reduced ALM index. Although BDI-II scores were generally higher for those with reduced ALM index, the differences were not statistically different. On the other hand, HADS scores were similar for those with normal and reduced ALM index. General health and average health SF36 scores were greater for those men with a normal ALM index. On univariate analysis, we found no associations with fat mass index and depression, anxiety or general health scores, in keeping with a previous report which measured total body fat [34]. On the other hand, patients with reduced ALM index had higher BDI-II scores, and higher HADS scores, showing an association between reduced appendicular muscle and increased depression and anxiety. Whereas higher SF36 self-reported scores, suggestive of better general health were associated with greater appendicular muscle mass. Patients with greater muscle mass would be expected to be more physically active, with reports also observing a link between greater muscle mass and less co-morbidity [35,36].

We chose cut offs for the BDI-II and HADS scores based on previous reports [37,38]. Smaller single centre studies from other countries have suggested alternative cut off points [39]. Logistic regression models showed an association between high self-reported BDI-II scores suggestive of depression and female gender and duration of haemodialysis treatment. Longer duration of haemodialysis is generally associated with loss of residual renal function, which has been previously reported to be a factor associated with increased depression [40]. Although reduced ALM (sarcopenia) was retained within the model, it was not independently associated with a high BDI-II score. ALM index was independently associated with a high anxiety distress score,

with lower ALM index associated with greater anxiety and distress, as was C reactive protein. However, the strength of these models was weak with an r^2 value of <0.15, and as such these associations should not be over interpreted. However, our results would be supported by reports of isometric exercise in patients with chronic kidney disease improving [41].

We report an association between reduced appendicular muscle mass measured by segmental bioimpedance and increased self-reported depression, anxiety and lower general health. Our study can only report an association, and whether treatment programs designed to improve muscle mass, lead to reduced levels of depression, and anxiety and improved perceived general health, or whether effective treatments for depression and anxiety might conversely improve muscles mass remains to be determined.

The authors have no conflicts of interest

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Table 1. Patient cohort demographics. Body composition results post dialysis. Serum haemoglobin and chemistries pre-dialysis. Results expressed as integer, percentage, mean ±standard deviation or median and interquartile range.

variable	
Weight pre-dialysis kg	73.7 ±18.9
Weight post-dialysis kg	72.1 ±18.9
Body mass index kg/m^2	25.2 (22.8-28.6).
Extracellular water/total body water pre-dialysis	39.8 ±1.4
Extracellular water/total body water post-dialysis	39.0 ±1.6
Fat mass kg	22.2 (15.3-28.4)
% body fat	31.4 (22.2-38.2)
Fat free mass kg	47.4 (42.3-56.5)
Fat free mass index kg/m^2	17.8 (15.9-19.2)
Appendicular lean mass kg	19.1 (16.2-24.3)
Appendicular lean mass index kg/m^2	6.98 (6.22-8.10)
Haemoglobin g/L	114.0 ±14.5
Urea mmol/L	18.4 ±4.6
Creatinine umol/L	714 (584-886)
Albumin g/L	40.3 ±3.4
Cholesterol mmol/L	4.1 ±1.0
C reactive protein mg/L	5 (2-12)
Calcium mmol/L	2.39 ±0.15
Phosphate mmol/L	1.47 ±0.39
Glucose mmol/L	6.2 (5.2-7.6)
B2 microglobulin mg/L	25.6 (20-32.5)
Dialysis urea reduction ratio	74.5 ±7.5
On-line sessional dialysis clearance	1.43 ±0.22
Past history myocardial infarction %	11.5
Coronary artery bypass surgery %	13.3
Coronary artery stenting %	8.0
Peripheral vascular disease %	3.5
Transient ischaemic attack %	7.1
Cerebrovascular disease %	17.7
Diabetes mellitus %	39.8
Stoke-Davies co-morbidity score	1 (0-2)
Hospital Anxiety Depression Score total	10 (5-16.5)
Beck Depression Inventory -II	11 (4-17)
Short Form 36 physical functioning	45 (15-65)
Short Form 36 physical role	0 (0-50)
Short Form 36 energy	50 (30-60)
Short Form 36 general health	35(30-40)
Short Form 36 average	43.3(36.6-48.4)

Table 2. Patients were divided into those with normal or reduced appendicular lean mass index (ALMI). Beck Depression Inventory -II (BDI-II), Hospital Anxiety Depression Score (HADS), Short Form 36 (SF36). Results expressed as integer, or median and interquartile range. * $p<0.05$ vs normal ALMI.

	Normal ALMI	Reduced ALMI	Normal ALMI	Reduced ALMI
variable	female	female	male	male
number	15	5	34	34
HADS anxiety	7(3-8)	7.5(5.5-8.0)	3(1-7)	4(0-7)
HADS depression	8(6-9)	8.5(4.5-10)	4(1-6)	4(2-8)
HADS total	14(8-20)	15(10-18)	7(4-12)	9(3-15)
BDI-II	13(9-17)	20(10-20)	6(2-12)	10(6-15)
SF36 physical functioning	45(15-55)	20(25-50)	57.5(30-85)	45(20-65)
SF36 physical role	0(0-0)	12.5(0-37.5)	25(0-75)	0(0-25)
SF36 emotional	66.7(0-100)	83.3(33.3-100)	100(100-100)	100(33.3-100)
SF36 energy	50(35-55)	32.5(25-45)	50(45-60)	55(35-65)
SF36 emotional wellbeing	72(60-84)	76(64-84)	84(64-92)	78(68-88)
SF36 social functioning	50(37.5-50)	87.5(56.3-100)	93.8(50-100)	62.5(37.5-75)*
SF 36 pain	65(45-90)	41.3(17.5-78.8)	88.8(70-100)	90(45-100)
SF36 general health	35(30-40)	27.5(22.5-57.5)	55(35-80)	40(25-60)*
SF36 average	43.3(36.6-48.4)	47.5(32.1-64.6)	68.8(51.9-78.8)	52.4(42.8-72.3)*

Table 3.
Univariate Spearman association between body composition and self-reported questionnaires. Beck Depression Inventory -II (BDI-II), Hospital Anxiety Depression Score (HADS), Short Form 36 (SF36).

variable	questionnaire	r	p
Fat free mass index	SF36 physical functioning	0.32	<0.001
	SF36 social functioning	0.26	0.013
Soft lean mass index	SF36 physical functioning	0.31	0.006
	SF36 physical role	0.22	0.042
Appendicular lean mass index	BDI-II	-0.29	0.008
	HADS depression	-0.27	0.012
	HADS total	-0.22	0.041
	SF36 physical functioning	0.34	0.001
	SF36 physical role	0.26	0.016
	SF36 energy	0.22	0.043
	SF36 general health	0.26	0.019

Table 4. Logistic regression models using a BDI-II cut point ≥16 and HADS cut point ≥8. Unstandardised beta coefficient (β coeff), standard error (StE), standardised beta coefficient (St β), 95% limits of agreement (95 LA). Duration of haemodialysis treatment (Vintage), Appendicular lean mass (ALM), reduced ALM index meets criteria for sarcopenia. Models, r^2 0.181, adjusted r^2 0.148; and r^2 0.154, adjusted r^2 0.121, respectively.

	B coeff	StE β	St β	t	95% LA	p
BDI model						
Female gender	0.35	0.12	0.32	2.9	0.9 to 1.0	0.004
Log Vintage months	0.16	0.06	0.28	2.6	1.0 to 1.1	0.010
Reduced ALM index	0.18	0.09	0.26	1.9	0.9 to 1.1	0.060
HADS model						
ALM index kg/m^2	-0.11	0.04	-0.31	-2.8	-1.9 to -0.3	0.007
Log CRP mg/L	0.21	0.07	0.25	2.3	0.03 to 0.39	0.023
Urea mmol/L	0.02	0.01	0.19	1.8	-0.01 to 0.05	0.080