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ORIGINAL ARTICLE

Using a generic definition of cachexia in patients with kidney disease receiving haemodialysis: a longitudinal (pilot) study

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ABSTRACT

Background. Research indicates that cachexia is common among persons with chronic illnesses and is associated with increased morbidity and mortality. However, there continues to be an absence of a uniformed disease-specific definition for cachexia in chronic kidney disease (CKD) patient populations.

Objective. The primary objective was to identify cachexia in patients receiving haemodialysis (HD) using a generic definition and then follow up on these patients for 12 months.

Method. This was a longitudinal study of adult chronic HD patients attending two hospital HD units in the UK. Multiple measures relevant to cachexia, including body mass index (BMI), muscle mass [mid-upper arm muscle circumference (MUAMC)], handgrip strength (HGS), fatigue [Functional Assessment of Chronic Illness Therapy (FACIT)], appetite [Functional Assessment of Anorexia/Cachexia Therapy (FAACT)] and biomarkers [C-reactive protein (CRP), serum albumin, haemoglobin and erythropoietin resistance index (ERI)] were recorded. Baseline analysis included group differences analysed using an independent *t*-test, dichotomized values using the χ^2 test and prevalence were reported using the Statistical Package for the Social Sciences 24 (IBM, Armonk, NY, USA). Longitudinal analysis was conducted using repeated measures analysis.

Results. A total of 106 patients (30 females and 76 males) were recruited with a mean age of 67.6 years [standard deviation (SD) 13.18] and dialysis vintage of 4.92 years (SD 6.12). At baseline, 17 patients were identified as cachectic, having had reported weight loss (e.g. >5% for >6 months) or BMI <20 kg/m^2 and three or more clinical characteristics of cachexia. Seventy patients were available for analysis at 12 months (11 cachectic versus 59 not cachectic). FAACT and urea reduction ratio statistically distinguished cachectic patients ($P = 0.001$). However, measures of weight, BMI, MUAMC, HGS, CRP, ERI and FACIT tended to worsen in cachectic patients.

Conclusion. Globally, cachexia is a severe but frequently underrecognized problem. This is the first study to apply the defined characteristics of cachexia to a representative sample of patients receiving HD. Further, more extensive studies are required to establish a phenotype of cachexia in advanced CKD.

Keywords: cachexia, definition, haemodialysis, longitudinal analysis, phenotype

INTRODUCTION

Cachexia is present in a range of chronic illnesses, including chronic kidney disease (CKD). It is associated with increased morbidity and mortality, including lower quality of life, increased depression, higher rates of hospitalization and increased

KEY LEARNING POINTS

What is already known about this subject?

- Globally, cachexia is a severe but frequently underrecognized problem.
- Cachexia is associated with increased morbidity and mortality, including lower quality of life, increased depression, higher rates of hospitalization and increased risk of death from cardiovascular disease.
- Cachexia is present in a range of chronic illnesses, including cancer, cardiac disease, chronic obstructive pulmonary disease, rheumatoid arthritis and chronic kidney disease. However, there is limited evidence about the presence of cachexia in end-stage renal disease.

What this study adds?

- According to a consensus (generic) definition, cachexia is prevalent in patients with renal disease receiving haemodialysis (HD).
- This is the first study to apply a consensus definition of cachexia to a population of patients with renal disease and receiving HD.
- This study helps to demonstrate the prevalence of cachexia in ESRD, including the impact on quality of life.
- Also, this study helps us to understand the challenges of recruiting and retaining patients within longitudinal research in this patient group.

What impact this may have on practice or policy?

- Further research is required to understand if cachexia can be identified as binary (present/absent) or still needs to be considered a process of bodily wasting in renal disease.
- Overall, given the impact of cachexia on quality of life in ESRD and the associated high mortality, it is imperative to develop a robust definition to allow for future feasibility testing of interventions for cachexia currently absent from renal guidelines.

risk of death from cardiovascular disease [1]. Several operational definitions exist for cachexia regarding it as the most severe stage of protein-energy wasting (PEW) to a stand-alone disorder [2,3]. PEW and cachexia tend to be used interchangeably in the literature [4], as both disorders have overlapping characteristics. However, research has led to the development of a clinical phenotype for cancer cachexia and other chronic illnesses [5]. The prevalence of cachexia ranges from 5% in rheumatoid arthritis (severe) to 80% in cancer patients [6]. Wasting syndromes are also common in renal disease and are reported across all CKD stages, although it is less common in early CKD (5–9%) compared with advanced CKD stages (20–30% in Stages 4–5). The highest prevalence of wasting is in end-stage renal disease (ESRD) and those receiving maintenance dialysis treatment [7]. Therefore the ability to accurately assess and monitor cachexia in CKD is essential.

Diagnosing wasting in CKD by estimating measurements of non-oedematous tissue and muscle mass is challenging [8]. Advanced CKD is associated with multiple symptoms, particularly those managed by haemodialysis (HD) [9], who experience significant and complex changes to their nutritional status and body composition. These alterations to body composition can further confound identifying and diagnosing cachexia [10]. Cachexia in CKD (e.g. tissue weight loss) is often masked (e.g. by oedema/fluctuating hydration status). These factors, alongside the lack of a disease-specific definition for cachexia in CKD, help to explain why it is less commonly recognized in clinical practice [7].

Evans *et al.* [3] proposed generic criteria for diagnosing cachexia in chronic illness with appropriate assessment and cut-off points that principally requires evidence of unexplained weight loss, low muscle mass and low muscle strength [e.g. by handgrip strength (HGS)], as well as abnormal biochemistry (Table 1). Evidence is needed to establish if this definition is useful and specific to HD patient populations, as currently there is no standardized phenotype for the identification and assessment of cachexia in ESRD. Therefore the aim of this study was to identify cachexia in patients with ESRD receiving HD using the definition of Evans *et al.* [3] and then follow-up on these patients for 12 months.

MATERIALS AND METHODS

We report a longitudinal study with adult HD patients between September 2017 and April 2019 who attended two nephrology units within the UK. Approximately 310 patients with ESRD receiving HD are cared for in the two nephrology sites. Prospective sample size was calculated. This study recruited 106 patients, which satisfied an 80% confidence level. Patients were eligible for inclusion if they had a confirmed diagnosis of ESRD [estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2] and were receiving HD, were able to read and write English and were >18 years of age (no upper age limit). Patients were excluded if they were Stage 1–4 CKD, Stage 5 CKD not receiving HD, lacked the capacity to give consent, were <18 years of age or were non-English speaking.

This research collected data [weight, muscle mass, strength, biomarkers, quality of life (Kidney Disease Quality of Life 36)] via assessments at the point of entry into the study and every 2 months for 1 year. A single researcher carried out all assessments. From these data, a diagnosis of cachexia was made using the definition proposed by Evans *et al.* [3] for cachexia in chronic illness. A minor modification was included and has been validated in the literature [7]. This included weight loss $\geq$5% for >6 months and $\geq$10% for >12 months, allowing for longitudinal assessment (beyond 6 months) [3].

Table 1. A generic definition for cachexia [3] and recommended cut-offs

Criteria [3]			Cut-off points
Primary criteria	Weight loss or a low BMI		Weight loss ≥5% for >6 months and ≥10% for >12 months*; Or a BMI <20kg/m^2
AND	Decreased muscle strength		Handgrip strength (i.e. <27 kg (m)/ <16 kg (f))
Three of the following secondary criteria	Fatigue		Severe fatigue (i.e. FACIT < 30)
	Anorexia		Poor appetite (i.e. FAACT < 32)
	Low fat-free mass index		Lean tissue depletion (MUAMC i.e. <23.8 cm (m)/ <18.4 cm (f))
	Abnormal biochemistry	Increased inflammation	C-reactive protein (CRP) > 5.0 mg/L
		Anaemia	Haemoglobin < 120 g/L
		Low serum albumin	Serum albumin < 32 g/L

*minor adapted criterion [7]

Ethics

Governance approval for the study was obtained from the host institutions and ethical approval from the Office for Research Ethics Committees Northern Ireland prior to the study commencing (Research Ethics Committee reference 16/NI/0233 and UK Health Research Authority). All patients provided written informed consent and the study was conducted in accordance with the principles set out in the Declaration of Helsinki.

Assessments

At baseline, demographic data and cachectic status [e.g. weight loss/body mass index (BMI), primary renal disease, comorbidities] were recorded. The percentage weight change was evaluated at enrolment using medical records. Standard biochemical parameters, including dialysis efficiency [urea reduction ratio (URR)] and eGFR were also recorded. Baseline and longitudinal assessment included twice-monthly assessments (±1 week) of weight loss ≥5% for >6 months and ≥10% for >12 months or a BMI <20 kg/m^2. Additional criteria included lean tissue depletion [using mid-upper arm muscle circumference (MUAMC)], reduced HGS, reduced appetite, fatigue, abnormal biochemistry, increased inflammatory markers [C-reactive protein (CRP) ≥5.0 mg/L], anaemia (haemoglobin ≤120 g/L) and low serum albumin (≤32 g/L). The erythropoietin resistance index (ERI) was also calculated as a surrogate marker for anaemia in this patient cohort [weekly erythropoiesis-stimulating agent (ESA) dose/weight (kg) × haemoglobin level (g/L)]. If the patient died at 6 months, their data were excluded from the longitudinal analysis.

Bioelectrical impedance analysis (BIA)

BIA was used to measure the phase angle using a calibrated dual-frequency (5 and 50 kHz) Bodystat 1500 MDD device (Bodystat, Isle of Man, UK). A standard protocol was followed with all assessments taken in the post-dialysis period to control for variation in fluid status. Measurements were taken in the supine position, with electrodes attached on the hand and foot contralateral to the side of the arteriovenous fistula, and at constant room temperature. Patients with any implantable electronic devices (such as pacemakers) were excluded as per the manufacturer's guidelines. For those patients who could not complete the BIA, a measure of BMI was calculated using the clinical formula: weight (kg)/height (m^2).

Muscle mass (MUAMC)

Mid-arm circumference (MAC) and triceps skinfold (TSF) thickness (TSF in triplicate and the average calculated) were measured in the non-fistula arm using a tape measure and Harpenden skinfold caliper set, respectively. The MUAMC was calculated using the formula: MAMC (cm) = MAC (cm) − 0.314 × TSF (mm). Suitable cut-point values designated the 5th percentile as an appropriate cut-point for low MUAMC using normative values (i.e. <23.8 cm for males and <18.4 cm for females) [11, 12].

Muscle strength (HGS)

Muscle function includes a range of measures of power, strength, endurance and fatigability. HGS (muscle strength) was recorded using a standard protocol (dominant arm, seated position with elbow at 90°, allowing three attempts) [13] and using a dynamometer (Jamar dynamometer, Patterson, Nottingham, UK). Specific cut-off points were applied based on the European Working Group for Sarcopenia in Older People (EWGSOP) for muscle strength (<27 kg for males and <16 kg for females) [14].

Fatigue [Functional Assessment of Chronic Illness Therapy (FACIT)]

Fatigue was recorded using the FACIT version 4 [15]. Brown *et al.* [16] reported strong correlations between the 'chair-rise' time test and FACIT, suggesting it is a reliable measure of physical function. Lower scores of the FACIT subscale refer to lower function and thus increased fatigue. The optimal cut-off value for FACIT is <30 [17].

Anorexia [Functional Assessment of Anorexia/Cachexia Therapy (FAACT)]

Appetite was recorded using the FAACT [18]. Lower scores on FAACT reflect poor appetite. The optimal cut-off value for the FAACT is <32 [19].

Analysis

Statistical analysis was performed using SPSS 24 (IBM, Armonk, NY, USA) [20]. Baseline analysis included descriptive

Table 2. Baseline characteristics

Characteristics	All ($N = 106$)	Cachectic ($n = 17$)	Not cachectic ($n = 89$)	Significance
Sex (female), *n* (%)	30 (28)	7 (41)	23 (25.8)	NS
Age (years), mean ± SD	67.62 ± 13.18	66.71 ± 11.44	67.80 ± 13.54	NS
Age >65 years, %	63	64	59	–
Years on dialysis, mean ± SD	4.92 ± 6.12	2.78 ± 3.04	5.34 ± 6.49	NS
Catheter access (versus central line), %	84.9	76.5	86.5	NS
CCI score, mean ± SD	6.10 ± 2.30	6.65 ± 1.73	6.00 ± 2.39	NS
Diabetes, %	52	24	56	-
Cancer, %	25	18	26	-
BMI (kg/m^2), median (IQR)	28.0 (23.0–31.3)	23.0 (20.0–29.5)	28.0 (24.0–32.0)	NS
Weight (kg/m^2), median (IQR)	81.3 (65.2–91.2)	62.2 (55.1–84.7)	82.6 (67.4–93.0)	NS
URR, median (IQR)	0.73 (0.69–0.77)	0.75 (0.72–0.81)	0.73 (0.68–0.77)	<0.001
eGFR, median (IQR)	8.2 (6.5–6.9)	6.8 (5.5–6.8)	8.6 (6.85–10.7)	NS
Phase angle,[a] median (IQR)	5.1 (4.3–5.7)	5.5 (4.8–5.8)	4.9 (4.15–5.7)	NS
MUAMC (m/f), median (IQR)	25.0 (22.9–27.5)/ 24.1 (21.0–25.9)	22.6 (21.6–23.4)/ 23.2 (20.7–29.3)	25.6 (23.6–28.2)/ 24.2 (21.1–25.6)	NS
HGS (kg) (m/f), median (IQR)	21.8 (17.4–27.3)/ 13.6 (10.7–21.0)	17.5 (11.6–22.5)/ 13.9 (12.9–24.8)	22.1 (17.8–28.5)/ 13.3 (10.5–18.9)	NS
CRP (mg/L), median (IQR)	10.6 (3.0–19.6)	17.0 (6.8–31.8)	8.0 (3.0–17.8)	NS
Serum albumin (g/L), median (IQR)	37.5 (34.0–40.0)	37.0 (34.0–39.5)	38.0 (34.5–40.0)	NS
Haemoglobin (g/L), median (IQR)	113.0 (104.0–119.0)	113.0 (104.5–124.0)	113.5 (103.5–119.0)	NS
ERI, median (IQR)	37.9 (16.3–82.5)	43.3 (31.8–92.4)	31.6 (15.1–82.7)	NS
FAACT (ACS), mean ± SD	37.24 ± 7.39	30.53 ± 10.48	38.52 ± 5.90	0.001
FACIT, mean ± SD	32.53 ± 12.27	27.00 ± 12.21	33.58 ± 12.07	NS
KDQOL-36 symptoms/problems list, mean ± SD	78.71 ± 15.24	68.01 ± 17.34	80.76 ± 14.00	NS
KDQOL-36	78.36 ± 20.44	67.47 ± 26.17	80.44 ± 18.62	NS
Effect of kidney disease, mean ± SD				
KDQOL-36	44.99 ± 29.48	40.80 ± 24.72	45.79 ± 30.37	NS
Burden of kidney disease, mean ± SD				
KDQOL-36 PCS SF-12, mean ± SD	37.92 ± 10.37	33.29 ±11.04	38.80 ± 49.25	NS
KDQOL-36 MCS SF-12, mean ± SD	48.25 ± 11.91	43.01 ±13.96	49.25 ± 11.29	NS

[a]Reported by $n = 87$.

KDQoL-36, 36-item Kidney Disease Quality of Life; PCS SF-12, physical component score 12-item Short Form Health Survey; MCS SF-12, mental component score 12-item Short Form Health Survey; CCI, Charlson comorbidity Index; m/f, male/female.

Table 3. Attrition information for all patients (and those identified as cachectic at baseline) at 12 months

Group	Total	Died	Transplant	Lost to follow-up	Withdrawn	HPD	Event free
All, *n* (%)	106 (100)	13 (12)	14 (13)	1 (1)	5 (5)	3 (3)	70 (66)
Cachectic at baseline, *n* (%)	17 (16)	5 (29)	0 (0)	1 (6)	0 (0)	0 (0)	11 (65)
Not cachectic at baseline, *n* (%)	89 (84)	8 (9)	14 (16)	0 (0)	5 (6)	3 (3)	59 (66)

HPD, home peritoneal dialysis.

results at each time point, which are presented as mean ± standard deviation (SD). Sex-specific cut-points were applied to relevant data (HGS, MUAMC). Baseline analysis included group differences analysed using an independent *t*-test. Dichotomized values were compared using the χ^2 test. Longitudinal analysis was conducted using repeated measures analysis. Values were significant for all analyses at P-value <0.05 with Bonferroni correction where appropriate.

Ethical approval

This study received ethical approval and consent from the Office of Research Ethics Committees Northern Ireland (REC:16/NI/0233). All participants received a patient information sheet detailing the study and were required to complete a written consent form to participate in the study.

RESULTS

Baseline results

A total of 106 patients (30 females and 76 males) were recruited and, at baseline, 17 patients were identified as having cachexia: 13 patients had >5% weight loss and 4 had a recorded BMI <20 kg/m^2. All 17 patients had three or more clinical

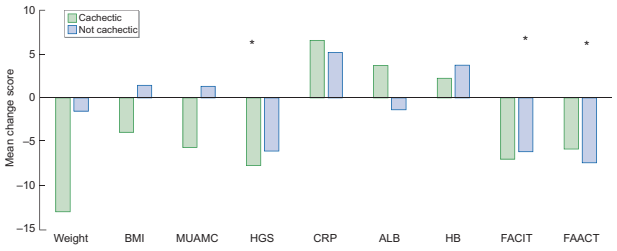

FIGURE 1: Mean change scores of clinical characteristics of cachexia between baseline and follow-up ($n = 70$). *Indicates a statistically significance difference. C, Cachectic; NC, Not cachectic; Alb, serum albumin; Hb, haemoglobin.

characteristics of cachexia [3]. Eighty-nine patients were identified as not cachectic.

Table 2 provides mean baseline scores for all patients. Bonferroni correction was applied. Cachexia prevalence in this patient sample was 16% ($n = 17$). Independent *t*-test demonstrated that only URR ($P < 0.001$) and FAACT ($P = 0.001$) were significantly different at baseline between those with cachexia and those without. URR was higher in patients with cachexia than in those without cachexia [mean 1.2 (SD) 1.95 vs. 0.71 (0.10)]. Appetite was poorer in patients with cachexia than those without cachexia [mean 30.53 (SD) 10.48 vs. 38.52 (5.90)].

Longitudinal results

The majority of patients ($n = 70$) were included at the final assessment point (Time 6; Table 3). Thirty patients identified at baseline as not cachectic were not followed up (8 died, 14 were transplanted, 5 withdrew and 3 started home peritoneal dialysis). Six patients identified at baseline as cachectic were not followed up (five died, one was lost to follow-up). Longitudinal follow-up included 11 patients identified as cachectic at baseline and 59 patients identified as not having cachexia (Supplementary file 1).

Figure 1 shows significant changes in HGS, FACIT and FAACT at 12 months for the 70 patients who remained in the study. After normality checks, a repeated measures analysis was conducted using Greenhouse–Geisser correction for the patient groups. The cachectic group showed a significant main effect of time on HGS ($P < 0.001$), FACIT ($P < 0.001$) and FAACT ($P < 0.001$). *Post hoc* tests with Bonferroni correction revealed significant decreases for FACIT (baseline vs. Time 6; $P < 0.01$) and FAACT (baseline vs. Time 6; $P = 0.01$). A significant decrease in HGS was reported (baseline vs. Time 6; $P < 0.01$). The non-cachectic group showed a significant effect of time on HGS ($P < 0.001$), FACIT ($P < 0.001$) and FAACT ($P < 0.001$). FACIT and FAACT scores declined significantly between baseline and Time 6 ($P = 0.02$ and $P = 0.01$, respectively). HGS also significantly decreased (baseline vs. Time 6; $P < 0.05$).

DISCUSSION

This study assessed whether the criteria for cachexia, proposed by Evans *et al.* [3], could be applied to a representative sample of HD patients at baseline with subsequent follow-up every 2 months to a final time point at 12 months. The study evaluated whether cachectic characteristics were present at baseline and to what extent these measurements of cachexia changed over time. The results suggest that cachexia is common in ESRD patients treated with HD, as 16% of the sample were classified as cachectic at baseline. Reduced appetite and low HGS helped to distinguish between cachectic and non-cachectic patients, whereas low muscle mass, fatigue and biomarkers were not. However, despite a lack of significant differences, overall measures of weight, BMI, MUAMC, HGS, CRP, ERI, FAACT and FACIT were worse in those identified as cachectic at baseline, although anaemia and increased inflammatory markers were common in both groups. Conversely, neither the cachectic or non-cachectic groups had significant hypoalbuminemia. Surprisingly, dialysis adequacy was significantly better in the cachectic group. However, measurements of URR can vary considerably from treatment to treatment [21], therefore alternative measures (e.g. Kt/V) are required.

Cachectic phenotype

In the absence of recorded weight loss, a BMI $<20\,kg/m^2$ can be used as the primary criterion for cachexia [3]. It has been useful in this patient cohort at identifying patients with 'kidney cachexia'. However, BMI requires further investigation. More than 60% of this patient sample was either overweight or obese, which is consistent with other renal studies [22]. It has been suggested that BMI cut-offs may misrepresent the degree of adverse outcomes in older populations [23, 24] and caution should be used when interpreting results.

MUAMC provides a measure of muscle mass. After Bonferroni correction, no significant differences between patient groups at baseline were reported. However, clinical cut-offs for low muscle mass were reached, indicating muscle catabolism is common in this cohort. The longitudinal assessment highlighted a declining trajectory; however, this was not statistically significant between baseline and follow-up. There is a clear need to routinely monitor muscle mass in CKD. However, gold standard assessment measures, although more accurate (e.g. dual-energy X-ray absorptiometry) [8], are difficult to incorporate into routine clinical practice in HD patients. Impedance vector analysis was not possible due to the small sample size and respective missing data. However, this technique is useful in CKD patient populations to assess muscle mass independent of the hydration status [25].

Mean scores of muscle strength, measured by HGS, were low in all groups and met clinical cut-offs at baseline for cachectic males but not females. This may be explained by the small number of females recruited. The longitudinal analysis demonstrated a further statistically significant decline in HGS in both groups. According to the EWGSOP recommended criteria, this cohort exhibited clinically low levels of grip strength, an

important indicator of sarcopenia and frailty (14; <27 kg for males, <16 kg for females) highlighting potential overlap with other disorders [26]. It is also argued that CKD accelerates the aging process, which helps to explain why the frailty phenotype is commonly reported in CKD patient populations [27]. Such clinical overlap with cachexia requires further investigation in CKD.

CRP is the most widely agreed upon biomarker of metabolic abnormality in cancer cachexia [28]. Results from this study indicate that patients with ESRD receiving HD have elevated CRP levels at multiple time points, consistent with chronic inflammation. Evidence suggests that inflammation in patients with advanced CKD is multifactorial and not uncommon [29]. Therefore the cut-off value for CRP levels in an ESRD population needs to be revised to a level >5 mg/L.

Levels of serum albumin were not useful in identifying patients with weight loss or cachexia. While albumin concentration is widely used to measure nutritional status, this is confounded in patients receiving HD. It is recommended that no single marker should be used to assess nutritional status in renal disease [30]. This is because serum albumin is influenced by a range of factors, including fluid balance status, proteinuria and acute inflammation [31]. Lower serum albumin levels are also associated with persistent systemic inflammation [32] and may decrease further as the chronic disease progresses [33]. Surprisingly, at baseline, albumin was found to be higher in the cachectic group, and this trend was observed at the end of the study. Fujiwara *et al.* [34] demonstrated that serum albumin can show substantial intraday variation, which may help to explain current findings and supports further assessment.

Similar to serum albumin, haemoglobin did not differ statistically between groups. Clinical practice guidelines suggest that haemoglobin levels in HD patients should be maintained within an optimal range of 100–120 g/L with the use of ESAs and intravenous iron. It is therefore not surprising that the mean haemoglobin levels of HD patients in this study were below the haemoglobin concentration of 120 g/L proposed as a marker for cachexia [3, 35]. Compared with the trajectory of the ERI, a surrogate marker for anaemia maintenance, haemoglobin was less useful as a cachexia marker in ESRD [36]. As CKD progresses, haemoglobin levels tend to decrease, necessitating the use of ESAs to increase haemoglobin and reduce the clinical impact of more severe anaemia. ERI scores were higher in cachectic patients, suggesting such patients require increased dosages of ESAs to remain within the optimal range of 100–120 g/L.

Patients categorized as cachectic at baseline also reported significantly poorer appetite. The longitudinal analysis also demonstrated appetite was significantly decreased for both groups by the end of the study. The prevalence of poor appetite or anorexia is reported to range between 25% and 61% in ESRD [37] and is associated with an increased likelihood of hospitalization, reduced quality of life and higher mortality [38]. However, to date, little is known about the direct or indirect impact of anorexia and its relationship with cachexia in ESRD. Prescribed drugs and supplements also interfere with appetite and should be carefully considered when using appetite as a predictor of cachexia. Despite this, the FAACT assessments are regarded as a valid tool in HD patients to discriminate anorexia [39].

Participants in the cachectic group also had greater fatigue at baseline, but this was not significantly different. This is not surprising, as fatigue is one of the most frequently reported symptoms and affects 60–97% of ESRD patients [40]. In addition, fatigue increased for both groups by the end of the study. When comparing mean scores for fatigue in cancer patients with cachexia, using the same validated tool as was used within this study (FACIT) [15], it is noteworthy that ESRD patients at risk of cachexia demonstrated fatigue similar to or greater than cachectic cancer patients. This helps to contextualize the impact of fatigue on ESRD populations and how this may be severely exacerbated in cachectic ESRD patients [41], an aspect not explored extensively in ESRD.

LIMITATIONS

The degree of attrition experienced over time in this study is similar to that of other renal studies [42], which helps to demonstrate the challenges of recruiting patients and retaining individuals within longitudinal research in this patient group. Of note, patients did not differ statistically on age or comorbidity levels. It is important to highlight that 52 patients were excluded at the recruitment stage for being 'very unwell' (deemed medically unfit to participate by clinical staff; see Supplementary file 2). Five patients were also withdrawn during the course of the study (Table 3), which may also cause bias. In addition, only one measure of the definition of Evans *et al.* [3] statistically distinguished cachectic and non-cachectic patients, a self-reporting measure of appetite. Future studies should consider objective assessments of nutritional intake. This study also had a relatively small sample size, with resultant limitations in interpreting the data. Survival analysis was not reported, however, 29% of cachectic patients died during the study compared with 9% of non-cachectic patients. There is a need to examine mortality and associated comorbidities in larger prospective medical data, taking account of cachexia. The strengths of this study include the recruitment and retention of 66% of the cohort, increasing the generalizability.

CONCLUSION

Globally, cachexia is a severe but frequently underrecognized problem. This is the first study to apply the known characteristics of cachexia to a representative sample of patients receiving HD. Overall, significant differences were limited; however, measures of muscle strength and reduced appetite are crucial in distinguishing between cachectic and non-cachectic patients. Additionally, measures of weight, muscle mass, BMI, CRP, ERI and fatigue were worse in those identified as cachectic at baseline. However, it is important to note this was a pilot study and future studies should aim to increase the sample size to provide further reliability and a 95% confidence interval addressing the aforementioned study biases. Further research is required to demonstrate if the definition of Evans *et al.* [3] identifies cachexia as binary (present/absent), moving away from a process [1]. Given the impact of cachexia on the quality of life of

patients with ESRD and the associated high mortality, it is imperative to develop a robust definition to allow for future feasibility testing of interventions for cachexia currently absent from renal guidelines.

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AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analysed during this study will be made available in the Queen's University Belfast repository (http://pure.qub.ac.uk/portal/en/datasets/search.html).

AUTHORS' CONTRIBUTIONS

J.R. is the principal investigator of this study. All authors assisted in the design of the study and revised and gave approval for the final version. C.M.K. and J.R. were responsible for data collection. C.M.K was responsible for the data analysis. C.M.K. and J.R. were responsible for the initial draft of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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