REVIEW

Wasting in Chronic Kidney Disease – a Complex Issue

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Abstract

Chronic kidney disease (CKD) has become a global health burden and is associated with increased morbidity and mortality. In particular, wasting is highly prevalent in later stages of the illness with muscle loss being a common problem. The aetiology and progression of this wasting is complex and multiple states have been identified linked to wasting in CKD. These include: 'malnutrition', 'disease-related malnutrition', 'protein-energy wasting', 'cachexia', 'sarcopenia', 'frailty' and 'muscle wasting'. The purpose of this paper is to review these terms in the context of CKD. Common features include weight loss, loss of muscle mass and muscle function principally driven by CKD disease specific factors and inflammatory mediators. Disease-related malnutrition would appear to be a more appropriate term for CKD than malnutrition as it take in to consideration disease specific factors such as inflammation for example. Frailty is commonly associated with age-related decline in physiological function. Development of novel screening tools measuring across multiple domains of nutritional status, muscle and physical function may be useful in CKD. Research into potential treatments are currently underway with focus on multi-modal therapies including nutrition, resistance training and anabolic drugs such as myostatin blockade and selective androgen receptor modulators. A better understanding of different states and terms may help guide assessment and treatment opportunities for patients.

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Introduction

Chronic kidney disease (CKD) is a serious medical condition associated with increased morbidity and mortality. The global incidence of CKD is estimated to be about 10% and found to be the 12th most common cause of death, accounting for 1.1 million deaths worldwide according to the 2015 Global Burden of Disease Study (1). Overall CKD mortality has increased by 31.7% over the last 10 years (1).

Patients with CKD tend to be multi-morbid and are treated with poly-medication (>4 medications) (2). Body wasting and specifically preferential loss of lean muscle mass are common occurrences in later stages of CKD due to alterations in multiple pathways controlling energy balance and protein turnover (3, 4). This loss of muscle mass increases the risk of poor clinical outcomes (5). Complexity arises with respects to differentiating different forms of wasting and muscle loss as a number of definitions exist (6). These include 'malnutrition', 'protein-energy wasting', 'cachexia', 'sarcopenia', 'frailty' and 'muscle wasting'. Different problems exist, for example a person with CKD may have muscle loss due to the effects of disease, ageing and physical inactivity (multiple factors) but be weight stable and even classified as obese (body mass index, BMI ≥ 30 kg/m^2) due to alterations in body composition (e.g. increase in fat mass and body water). Furthermore, the same individual may display physical functional impairments which may relate to frailty and increase the risk of disability (7). These issues all have to be taken into account when holistically assessing the individual with CKD. Therefore, a better understanding of the different terms is perhaps necessary and the current literature as it stands can become quite confusing. Furthermore, a better understanding of terms may help guide assessment and treatment opportunities for patients.

Malnutrition

Malnutrition has been defined in different ways by different consensus and working groups. Although malnutrition can technically be a state of nutrient or energy depletion (undernutrition) or excess (overnutrition), it is commonly considered in the current literature to be a state of undernutrition (8). Malnutrition due to starvation, disease or ageing can be defined as *"a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat mass) and body cell mass (BCM) leading to diminished physical and mental function and impaired clinical outcome from disease"* (8). The diagnostic criteria

for malnutrition, has been recently discussed in an ESPEN group consensus statement (8). Further, an International Guideline Committee was formed to differentiate the differences between a) pure chronic starvation, b) chronic disease-related malnutrition (DRM) and c) acute DRM (9). CKD clearly falls under the definition of chronic DRM. However, a specific term, 'protein-energy wasting' (PEW) syndrome in CKD was developed by the International Society of Renal Nutrition and Metabolism (ISRNM) (3, 4). This has been defined as a *"state of decreased body stores of protein and energy fuels (body protein and fat masses)"* which occurs progressively and is specific to CKD (3, 4). It differs from basic protein calorie restriction in that it accounts for the effects of heightened inflammation (similar to DRM), kidney dysfunction and the effects of dialysis on metabolism (3, 4). Prevalence rates are high in CKD stages IV-V (50-75%) and are closely associated with both increased morbidity/mortality risk and worsened quality of life (10).

A point of relevant discussion is that the BMI is used as an indicator of nutritional status although it cannot differentiate between fat mass, fat free lean tissue mass and water. However, the World Health Organisation (WHO) and European Society for Clinical Nutrition and Metabolism (ESPEN) have used 18.5 kg/m^2 as a suitable cut-off point to indicate malnutrition (8). In the CKD population there is overwhelming evidence of a BMI paradox whereby patients with an overweight and obese BMI have better clinical outcomes compared to normal weight (11). In fact, the ISRNM have suggested using a cut-off point of 23 kg/m^2 to indicate PEW (3). It has been suggested that the more extreme type of PEW is 'cachexia', whereby there is more severe body depletion. In the definition for cachexia a BMI cut-off of 20 kg/m^2 is used in combination with other parameters (12).

Cachexia

Cachexia is derived from the Greek 'kakos' and 'hexis' meaning 'bad condition/state'. It has been defined as "a complex metabolic syndrome associated with underlying illness and characterised by muscle loss, with or without loss of fat" (12). Cachexia is in many respects quite similar to chronic DRM and seen as an advanced from of PEW (3). It is common for anorexia, increased energy expenditure and increased protein breakdown to coexist in chronic disease conditions such as cancer, chronic heart failure and CKD (12). This therefore leads to increased weight loss and in particular the loss of BCM and skeletal muscle mass (SMM). Cachexia development is thought to be principally due to heightened chronic inflammation (circulating proinflammatory cytokines) (13). In CKD this may be due to a range of factors including inflammation due to CKD itself or reduced Glomerular Filtration Rate (GFR), for example: decreased clearance of proinflammatory cytokines oxidative stress, carbonyl stress, or coexistence of comorbid conditions and inflammatory factors related to dialysis treatment (3, 4). This is known to have an impact upon appetite inducing anorexia (alongside other CKD specific factors), reducing energy intake (3, 4). Coupled with raised resting energy expenditure and protein breakdown this leads to net tissue loss and muscle protein in particular (3). Dialysis appears to have a deleterious impact upon this process with dialysis vintage (length of time on dialysis) found to relate to poor nutritional status with a significant decline in body composition measures (14).

In terms of the diagnostic criteria for cachexia it includes a loss of 5% of more of body weight over 12 months (or BMI < 20 kg/m^2) plus 3 of 5 criteria including reduced muscle strength, fatigue, anorexia, reduced fat free mass index, and abnormal biochemistry (e.g. increased inflammatory markers) (12). See Table 1 for more details. Furthermore, a specific diagnosis has been developed for cancer cachexia (15), but none for CKD. In the diagnosis, weight loss is > 5% over the past 6 months, or BMI < 20 with any degree of weight loss > 2%. In addition, the diagnosis also considers a low appendicular skeletal muscle index, (males <7.26 kg/m^2; females <5.45 kg/m^2) and any degree of weight loss > 2%.

The fact that a very high proportion of patients with end-stage renal disease (ESRD) have wasting/cachexia (16) underscores the need to develop clear management strategies for this patient cohort; especially as to date no single agent has emerged as a beneficial treatment for cachexia (17). To progress this science forward, there is a need for large, well-controlled studies to determine the most appropriate approaches to managing cachexia in this population. Furthermore, prior to such studies it is essential that a disease specific definition for cachexia in renal disease is established to ensure continuity across future research activity (18, 19). Reid et al, 2016 discusses this issue in some detail distinguishing the differences between cachexia, PEW and sarcopenia in the ESRD population on dialysis (19).

Table 1. Diagnostic criteria for cachexia in adults (from Evans et al 2008)

Weight loss of at least 5%* in 12 months or less in the presence of underlying illness**, PLUS THREE of the following criteria:
Decreased muscle strength (lowest tertile)
Fatigue***
Anorexia****
Low fat-free mass index[#]
Abnormal biochemistry Increased inflammatory markers CRP (>5.0 mg/l), IL-6 (>4.0 pg/ml) Anemia (<12 g/dl) Low serum albumin (<3.2 g/dl)

*Edema-free

**in cases where weight loss cannot be documented a BMI <20.0 kg/m^2 is sufficient.

***Fatigue is defined as physical and/or mental weariness resulting from exertion; an inability to continue exercise at the same intensity with a resultant deterioration in performance.

****Limited food intake (i.e. total caloric intake less than 20 kcal/kg body weight/d; < 70% of usual food intake) or poor appetite.

[#]Lean tissue depletion (i.e. mid upper arm muscle circumference <10th percentile for age and gender; appendicle skeletal muscle index by DEXA (kg/m^2) <5.45 in females and <7.25 in males.

Sarcopenia

The concept of PEW and cachexia becomes more complicated due to the impact of ageing and frailty. Linked to this is the term 'sarcopenia', or the loss of muscle mass and function with ageing (20, 21). Sarcopenia has been defined as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death. Sarcopenia ('Sarx' + 'penia' = loss of flesh) was originally designated as being the age related loss of muscle, but recently it has encompassed the loss of muscle strength and function (20-22). In addition, there has been a lack of consensus on whether it should be used specifically for age-associated loss of muscle or due to any illness (21). The causes of sarcopenia may be multi-factorial and include altered endocrine function (e.g. reduced sex hormones and growth hormone production), chronic diseases (e.g. CKD), disuse, inflammation (e.g. high proinflammatory cytokines), insulin resistance and nutritional deficiencies (e.g. energy, protein and micronutrients) (19).

Sarcopenia is a major component of physical frailty and linked to worsening of clinical outcomes, including falls and disability (20, 21, 23). Typically, sarcopenia is measured in older people using functional measures of gait speed and hand grip strength and muscle mass by DEXA, imaging techniques or bioimpedance (20, 21). The 'Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls' (SARC-F) was recently developed as a symptom score to predict persons with sarcopenia at risk for poor functional outcomes (24). See Table 2 for details.

The relevance of sarcopenia in CKD is not fully understood and requires further study. In addition, the development of a CKD-specific definition has not been considered yet. However, many studies have shown that low muscle mass (as a component of sarcopenia) is found in CKD. For example, sarcopenia was measured (using muscle mass) in the Korea National Health and Nutrition Examination Survey (KNHANES), 2008–2011 and related to CKD staging (25). In the study a total of 11,625 participants aged 40 years or older underwent Dual-Energy X-ray Absorptiometry (DEXA) and had Appendicular Skeletal Muscle mass (ASM) estimated. ASM was then divided by weight (ASM/Wt) and used as a measure of sarcopenia. Low ASM/Wt was higher in those with lower eGFR and ASM/Wt and eGFR significantly correlated in both men and women. Pereira et al evaluated 287 CKD patients in stages 3-5 and found that sarcopenia prevalence measured by handgrip strength and reduced muscle mass by bioelectrical impedance analysis was shown to be a significant independent predictor of mortality (26).

Technically however, these previous studies were not strictly measuring age-related sarcopenia as subject participants were not only over 65 years of age. This is something of importance to be discussed as many studies have only measured muscle mass/lean mass and imply sarcopenia assessment. The reduction in muscle mass due to CKD may relate to PEW or cachexia and potentially the term of muscle wasting may be more relevant. This is something that requires further discussion by consensus groups. Souza et al investigated the prevalence of sarcopenia in CKD patients not yet on dialysis (n=100) in Brazil and used the criteria of the European Working Group on Sarcopenia in Older People (EWGSOP) and of the Foundation for National Institutes of Health (FNIH) Sarcopenia Project (27). The mean age of the group was 73.59 years. Those with sarcopenia were older, showed worse performance in activities of daily living (ADLs), had slower walking speeds, worse functional capacity, higher prevalence of physical inactivity, had higher BMIs, less lean mass in their lower limbs and less ALM when adjusted for BMI. Interestingly, they report higher BMIs (mean: 32.03 +/- 5.91) which may indicate a form of 'sarcopenic obesity'. This is in contrast to PEW and cachexia where body wasting accompanies muscle loss. It may be that this group which was not on dialysis may have symptoms which precede overt wasting accompanied with the highly catabolic

dialysis phase. A further important point highlighted by Souza et al is that sarcopenia may develop at earlier stages of CKD (27). This would indicate the importance of assessing muscle mass, strength and physical function early on in CKD diagnosis as patients could be greater risk of developing frailty and disability. Furthermore, it would be suspected that CKD increases the loss of muscle mass and function with ageing. Type 2 diabetes has also been shown to accelerate the decline in muscle mass, strength and functional capacity with ageing (28). A dutch study looked at 60 older men (71 +/- 1 years) with type 2 diabetes (T2DM) and compared them to 32 normoglycemic control patients (28). They found that leg lean mass and appendicular skeletal muscle mass was significantly lower in those with T2DM. In addition, leg extension and hand grip strength, and 'sit-to-stand' performance was also significantly reduced.

Hirai et al, recently reviewed sarcopenia and physical inactivity in patients with CKD (29). They suggested that sarcopenia induces physical inactivity through the loss of skeletal muscle, which in turn induces the loss of physical function, and increased physical inactivity accelerates the progression of sarcopenia. It must be also noted, that although understudied, psychiatric comorbidities such as depression may be common in CKD (30). Depression may have a negative impact on motivation to take part in physical activity/exercise, promoting physical inactivity although there is a paucity of research in this area.

Sarcopenia assessment as a component of frailty should be considered with CKD patients and has been discussed recently by Moorthi and Avin, 2017 (31). Sarcopenia has also been given an ICD-10 code meaning that it is recognised as a disease in its own right and this should assist the development of screening and treatment programs (32).

Table 2. SARC-F screen for Sarcopenia (from Malmstrom 2013)

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do have walking across a room?	None = 0 Some = 1 A lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0 Some = 1 A lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1-3 falls = 1 4 or more falls = 2

Frailty

Leading on from sarcopenia, frailty has been defined as a *'clinically recognizable state of increased vulnerability resulting from an ageing-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stressors is comprised'* (7, 23). There are currently two generally accepted frailty concepts which include 'multidimensional frailty' and 'physical frailty'. Multidimensional frailty includes psychological and social components, multimorbidity, and disability in addition to physical impairments. Physical frailty includes all physical functional components and heavily overlaps with sarcopenia. Infact, sarcopenia is now considered to be the biological substrate of physical frailty (33).

In the absence of a gold standard, physical frailty has been operationally defined by Fried et al. (7) as meeting three out of five phenotypic criteria indicating compromised energetics: low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss (Table 3).

Research has shown that chronic diseases such as CKD increase risk of frailty. Frailty is significantly associated with all stages of CKD and particularly with moderate to severe CKD (34). As discussed in a recent review by Musso et al, prevalence of frailty in hemodialysis patients is around 42% (35% in young and 50% in elderly) and incidence of pre-frailty is 29% (35). This leads to a 2.60-fold higher risk of mortality and 1.43-fold higher number of hospitalisation, independent of age, comorbidity and disability. Results from the United States Third National Health and Nutrition Examination Survey (NHANES III) found in a sample of 10, 256 people overall that frailty prevalence was 2.8%, however, in those with advanced CKD it was 20.9% (34). Reese et al, measured the short physical performance battery (SPPB) (includes standing balance, 4 meter gait speed and sit-to-stand test) and the five frailty elements in 1111 Chronic Renal Insufficiency Cohort participants (36). CKD severity

was associated with poor physical performance and frailty in a graded fashion. eGFR 30 – 59 (OR 1.45; p=0.024), eGFR 15 – 29 (OR 2.02; p=0.002) and eGFR <15 (OR 4.83; p < 0.001) were associated with worse frailty status compared with 60 ml/min/1.73m^2. Walker et al, performed a systematic review on the association of frailty and physical function in patients with non-dialysis CKD (37). They found that CKD was consistently associated with increasing frailty or reduced physical function. Furthermore, frailty in CKD patients was associated with a two-fold greater risk of dialysis and/or death.

A recent systematic review was performed looking at the relationship between CKD and physical frailty and cognitive impairment (38). They found clear evidence of a relationship between CKD and frailty and cognitive impairment. Further, in a recent multicentre Canadian study involving 385 stage 4-5 CKD patients, it was found that 61% had cognitive impairment (39).

The importance of recognising frailty and assessing frailty in CKD patients is becoming understood in the medical community, especially as it relates to disability outcomes and quality of life. The following years will be crucial in developing this field and treatment options (e.g. exercise and pharmacological therapies).

Table 3. Definition of physical frailty

Unintentional weight loss (10 lbs or more in a year)
Self-reported exhaustion
Weakness (measured by grip strength)
Slow walking speed
Low physical activity

A pre-frail stage, in which one or two criteria are present, identifies a subset at high risk of progressing to frailty.

Muscle wasting disease

Last of all, the term 'muscle wasting disease' (MWD) has been proposed as an umbrella term for muscle wasting due to acute (e.g. burns, sepsis etc) or chronic conditions (e.g. CHF, CKD, COPD etc) (6, 40). MWD is perhaps an important concept as it is an easy to understand term for both lay people and the scientific community. Furthermore, some patients with chronic conditions such as CKD may have overt muscle wasting and be at risk of frailty but not always show any significant weight loss (due to changes in body fat and body water), and hence not termed as having cachexia or PEW. This is highlighted in the sarcopenia study by Souza et al where it would appear that participants are suffering from sarcopenic obesity (27). This could be the effects of the illness combined with dietary protein restriction (therapeutic treatment for CKD) and lack of physical activity, thus having an unfavourable effect on muscle protein turnover and overall muscle mass. Therefore, the importance of measuring the SMM compartment and physical function (as with sarcopenia assessment) should be given some priority. One problem however relates to the measurement of the SMM. Gold standard techniques are expensive and not always available, e.g. MRI. Bioimpedance is inexpensive but there are concerns over the accuracy of the technique in CKD patients. However, Pereira et al used BIA for muscle mass assessment and other groups have also (20, 26).

Time will tell whether the MWD concept takes hold in the scientific community and globally is adopted.

Screening Tools

Many different tools have been developed to assess the states of malnutrition, cachexia and sarcopenia. However, the specific application to CKD has been limited to a few key tools.

The Subjective Global Assessment (SGA) is a tool that uses 5 components of a medical history (weight change, dietary intake, gastrointestinal symptoms, functional capacity, disease and its relation to nutritional requirements) and 3 components of a brief physical examination (signs of fat and muscle wasting, nutrition-associated alternations in fluid balance) to assess nutritional status (41). It was suggested for use in CKD by Steiber et al, (42). Campbell et al compared the SGA and other similar SGA-based assessment tools with body cell mass measurement (by total body potassium) in 56 stage IV and V pre-dilaysis CKD patients (70.2 +/- 11.6 years) and found that the original SGA was most accurate at predicting malnutrition (43). Gurreebun et al, considered one issue that the SGA is quite time consuming and compared using the SGA with standard measures of malnutrition such as BMI, serum albumin and history of weight loss in 141 HD patients (44). Measurement of SGA did not diagnose malnutrition in any patients who had not already been diagnosed by measurement of albumin, BMI, and weight loss. Therefore, it was found that the SGA did not provide any additional sensitivity to malnutrition assessment.

The malnutrition inflammation score (MIS) or Kalantar Score was developed to take into account the nature of the malnutrition inflammation complex syndrome (MICS) which commonly occurs in dialysis patients (45) . The MIS uses components of the SGA and the dialysis malnutrition score (DMS) and includes BMI, albumin and serum total iron binding capacity. The MIS

was shown to correlate with morbidity and mortality in 83 maintenance HD patients (44 men, 39 women; aged, 59 +/- 15 years) (45). Furthermore, the MIS, but not the SGA or DMS, correlated significantly with creatinine, hematocrit, and CRP level. The use of the MIS and other screening tools for PEW in CKD is discussed in a recent review (46). Other nutritional screening tools include the geriatric nutritional risk index (GNRI) which was developed as a less time consuming objective tool which utilises plasma albumin and body weight/ideal body weight ratio (47). The GNRI was compared in 422 HD patients to other nutritional risk tools such as the mini nutritional assessment short form (MNA-SF), nutritional risk score (NRS), malnutrition universal screening tool (MUST), malnutrition screening tool (MST), using the MIS as a reference (48). The GNRI was found to have the best ability to discriminate nutritional risk.

The cachexia algorithm developed by Evans et al, 2008 is based upon presence of a chronic illness (e.g. CKD) with weight loss of at least 5% in 12 months or less (or BMI <20 kg/m^2) and 3 out of 5 including; decreased muscle strength, fatigue, anorexia, low fat-free mass index and abnormal blood biochemistry (e.g. increased inflammatory markers and low serum albumin) (12). Therefore, this would be an extension to nutritional risk tools by including muscle mass measurement and functional strength. This is highly advantageous towards assessing sarcopenia, muscle wasting and frailty.

An assessment of physical function e.g. hand grip strength and gait speed is a useful indicator of sarcopenia in old age, and components of cachexia and frailty. Gait speed in particular has been shown to correlate with mortality. For example, Kutner et al, studied gait speed and clinical outcomes in 752 US HD patients (aged 20 to 92 years evaluated in 2009 to 2012 in 7 Atlanta and 7 San Francisco clinics in a US Renal Data System special study) (49). Worsening of gait speed was found to be associated with higher death rates, hospitalisation and ADL difficulty. Furthermore, Roshanravan et al, investigated the association between measures of physical performance and all-cause mortality in 385 participants with stage 2-4 CKD. Tests included handgrip strength, usual gait speed, Timed Up And Go (TUAG) test and 6-minute walking distance (50). They found that gait speed and TUAG predicted 3 year mortality in participants. In particular, that each 0.1-m/s decrement in gait speed associated with a 26% higher risk for death, and each 1-second longer TUAG associated with an 8% higher risk for death. Chang et al, found that handgrip strength was an independent predictor of renal outcomes in 128 CKD patients (51). Therefore, it would make sense to incorporate gait speed, hand grip strength and possibly physical function (e.g. SPPB) into an assessment strategy for CKD patients.

Measurement of muscle mass to detect muscle wasting in cachexia and sarcopenia could be advantageous in assessment protocols. Practically, fat free mass/muscle mass could be measured by DEXA if available (fat free mass or ALM) or by bioimpedance (52). Although, there are concerns raised about bioimpedance accuracy due to fluid status changes. Researchers may have to be mindful of this and consider completing bioimpedance measurements always post dialysis in an effort to keep consistency etc (52). Another obvious choice would be to measure mid arm muscle circumference (MAMC) which is part of the PEW criteria. This is a low cost method which is highly reproducible once the person testing has been appropriately trained. This has been used by Landi et al, to estimate sarcopenia in older people (357 older people over 80 years of age) and relate to physical performance and mortality (53). Further, in a US study with 792 HD patients it was shown that a higher MAMC was an independent predictor of better quality of life and greater survival (54).

Viewing the different criteria and algorithms developed for the different states it can be seen that there is clear overlap between them. For example, physical frailty may be a consequence of CKD and cachexia with weight loss, fatigue, anorexia and loss of strength being common. Low muscle mass or FFM is a component of PEW, sarcopenia and cachexia. Hence, developing a multi-domain screening tool which takes into account CKD malnutrition/PEW and cachexia alongside physical function domains should be considered. This could be graded to consider the spectrum of development of DRM and PEW into cachexia and frailty.

Potentially, a multi-domain screening tool could be developed which measures malnutrition and cachexia (e.g. BMI, weight loss, albumin), physical function (grip strength and gait speed). This could also include components of the SGA for malnutrition and SARC-F for sarcopenia. It would be advantageous to be able to both dissect individual components and identify a phenotype, e.g. cachectic and frail.

Precise and timely diagnosis/assessment and close monitoring of nutritional and functional status is important as in later stages of CKD, as malnutrition and muscle wasting may lead to worsening of clinical outcomes. The optimal strategy for assessment requires further study for the CKD population.

Treatments

Nutritional guidance and supplementation is an important aspect of therapy whereby modulation of calorie and protein intake (e.g. by oral supplementation) is essential. Energy intake in CKD patients should be assessed and be adequate to support needs and requirements, especially as DRM, cachexia and frailty is so common in CKD patients. The combination of anorexia and hypermetabolism due to CKD specific and non-CKD related factors, ultimately leads to a loss in tissue mass. Data has also shown that frailty is associated with lower energy intakes and weight loss for example (7, 23). Other factors including supplementation with anti-

inflammatory nutrients such as omega-3 fatty acids should be considered in CKD patients. Whether or not this would reduce inflammation-driven wasting is not known, however, omega 3 fatty acids have known beneficial effects on cardiovascular function and health (55). In addition, omega-3 fatty acids have been shown to reduce the risk of progression to ESRD (56)

The metabolite of the branched chain amino acid leucine, beta-hydroxy-beta-methylbutyrate (HMB) has been suggested as a potential supplement for reducing muscle loss. Its impact in CKD patients is unknown at present but a systematic review with meta-analysis of studies in older adults has been performed and indicates a positive effect on preservation of muscle mass (57). Future controlled studies will need to be performed in CKD.

Correction of metabolic acidosis by bicarbonate has also been suggested as a treatment for CKD. In particular, acidosis is believed to play a role in increasing muscle wasting by effects on the IGF-1 pathway and glucocorticoids. Abramowitz et al, showed in a small study of 20 participants that NaHCO3 treatment improved physical function (sit-to-stand test) and decreased urinary nitrogen excretion, although there was no effect on handgrip strength (58). Future well powered studies are required to test these results.

Vitamin D supplementation is another consideration for the CKD patient as vitamin D plays a role in muscle function and vitamin D deficiency is very common in CKD (59, 60). One study looked at vitamin D supplementation (50,000 IU once per week) in 25 stage 3-4 CKD and 47 stage 5 CKD patients with vitamin D deficiency (61). The study found that correction of deficiency improved physical performance tests, static and dynamic balance tests and isometric strength tests.

The evidence base to support bespoke management strategies for both sarcopenia and cachexia are at different levels of maturity. In sarcopenia there is empirical evidence that protein supplementation together with exercise can reverse muscle loss in the affected individuals (62-64). Furthermore, in particular essential amino acids and leucine-enriched protein supplementation has been found to be most beneficial (62). However, in cachexia the evidence base is less well developed. For example, in persons with ESRD who are receiving dialysis there is an association between under-nutrition and mortality (16). Data has suggested that protein supplementation during dialysis reduces inflammation and enhances physical function and quality of life (65-68). However, the evidence base on cachexia in ESRD remains in its infancy.

Resistance training (RT) is a key treatment for muscle wasting, sarcopenia and frailty (29). However, its specific application and use for cachexia is not well studied and urgently needs investigating in CKD patients. A feasibility study was performed for RT in CKD (69). The study recruited thirty eight patients and achieved an 87% completion rate. Progressive RT increased muscle cross sectional area, muscle volume, knee extensor strength and exercise capacity (shuttle walk test). Furthermore, a systematic review and meta-analysis on RT in CKD was performed by Cheema et al (70). Seven Randomised Controlled Trials (RCTs) had measurements on muscular strength, six on total body muscle mass and six on health-related quality of life (HR-QOL). The RCTs were found to provide solid evidence that RT improves muscle strength, mass and HR-QOL in CKD patients. Future studies will be necessary to examine the impact of RT on wasting, physical function and activities of daily living in CKD patients, e.g. for frailty.

The research literature supports the concept of a multidisciplinary approach to combat wasting and frailty. Nutrition, exercise and drug treatment strategies for CKD need further study. Pharmacological treatments have been discussed in different contexts. For example, in targeting frailty and sarcopenia the evidence base is currently in its infancy but this a topical area and indeed was recently focused upon by the International Conference on Frailty and Sarcopenia Research Task Force (71). Specific drugs discussed in the paper which may have the potential to improve muscle protein balance and muscle mass including the myostatin antagonists and the Selective Androgen Receptor Modulators (SARMS). Whether they show an ability to reduce wasting and improve muscle function in CKD is not yet known. Other drugs which may have therapeutic benefits to CKD include conventional anabolic steroids and new ghrelin mimetic drugs (72). However, these require further investigation.

Conclusion

CKD is a global health burden and is associated with differing poor nutritional status, wasting and muscle loss. DRM would appear to be a more applicable definition for malnutrition and an evidence based renal specific definition for cachexia should be developed. Sarcopenia and frailty are prevalent in CKD and require further investigation. Furthermore, whether the MWD concept should be considered alongside cachexia and sarcopenia in CKD is unknown at present. It is suggested that a multi-domain screening tool be developed to identify different components of malnutrition, wasting and muscle dysfunction, as each may well require different treatment modalities. Such treatments require investigation with greater emphasis on multimodal therapies which combine nutrition, exercise and drugs. These multimodal therapies require testing to ascertain the best treatments for these patient cohorts.

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