Disease Related Malnutrition in Chronic Kidney Disease

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Abstract (200 words)

Purpose of review: Disease related malnutrition has complex and multifactorial pathophysiology. It is common in patients with chronic kidney disease (CKD) and has a devastating impact on morbidity and mortality. Given the rising numbers of patients diagnosed with CKD, disease related malnutrition is an escalating clinical challenge. This review summarises current knowledge in relation to the development, screening and treatments for disease related malnutrition in CKD

Recent findings: New research has identified other potential causes for the development of malnutrition in CKD, including changes in taste and smell, and effects of polypharmacy. Screening and assessment studies have investigated different tools in relation to the new GLIM criteria. Different modalities of low protein diets and the potential use of pre and probiotics is being explored. Furthermore, the importance of nutritional support, and possibly exercise during dialysis is being examined in terms of reducing anabolic resistance and catabolism.

Summary: Further research is required to better understand the nuances of the pathophysiology of disease related malnutrition in CKD. This work should inform not only consistent terminology and the application of assessment tools specific to disease related malnutrition in CKD but also the development of novel interventions which reflect its multifaceted pathophysiology and impact.

Key words: Chronic Kidney disease, disease related malnutrition, cachexia, sarcopenia, protein energy wating

Introduction

Chronic kidney disease (CKD) has a substantial impact on global health. In 2017 there were over 697 million cases of CKD worldwide. It resulted in 7.3 million years lived with disability (YLDs); 28.5 million years of life lost (YLLs), 35.8 million disability-adjusted life years (DALYs) and global mortality from CKD diagnoses was 1.2 million (1). The number of deaths from CKD are expected to rise to between 2.2 million – 4 million by 2040 (2).

Nutritional status is paramount in CKD as nutritional deficiencies result in adverse outcomes including reduced functionality and reduced survival (3). Malnutrition is commonly defined as “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease” (4). Malnutrition can occur due to a number of causes including starvation, disease, muscle wasting due to immobility and ageing or social isolation, either as a single cause or in combination (5). Disease related malnutrition “is a complex syndrome resulting from inadequate intake of nutrients that does not fulfil the patient's physiological requirement and from a disease-related systemic inflammatory response” (5).

There can be confusion in relation to terminology associated with malnutrition. Terms such as cachexia, age-related sarcopenia, and protein energy wasting have been used interchangeable within the literature alongside malnutrition (3,6). Difficulties in distinguishing between syndromes can be compounded by an overlap in commonly associated criterion (7). For example, muscle wasting which is a criterion for malnutrition is also a criterion in protein-energy wasting (PEW), cachexia and sarcopenia (6). Distinguishing between each syndrome is necessary to ensure the correct treatment approach. Of note, most recently progress has been made in relation to PEW and cachexia, where it has been indicated that PEW and cachexia are closely related, and that PEW corresponds to initial stages of a continuum that may progress to cachexia. It has also been suggested that the term ‘kidney disease cachexia’ might be adopted (3). While disease specific progress has been made in some syndromes, others such as sarcopenia, the most common parameter for which is low muscle strength (8), to date does not have a disease specific definition for individuals with CKD.

Development of Malnutrition in CKD

Many factors interplay increasing the risk of malnutrition and PEW in CKD. These include a range of metabolic and endocrine abnormalities which develop due to impaired kidney function. For example, reduced erythropoietin , vitamin D, carnitine, testosterone, and thyroid hormone (9); (10). Insulin resistance is common which leads to impaired suppression of muscle protein breakdown (e.g. after a meal); as is growth hormone resistance which leads to a reduction in anabolic potential (e.g. reduced hepatic insulin-like growth factor (IGF)-1 production) (10). There are also disturbances in adipocytokines such as leptin and ghrelin which may impact upon hypothalamic regulation of appetite (11). Uremic toxins are known to play a key role in the induction of anorexia (12). This impairment of appetite in patients has also

been associated with higher mortality (12). In particular, inflammation plays a major role in the development of the PEW syndrome (13). Due to the strong relationship between malnutrition and inflammation, the term 'malnutrition inflammation complex' was developed (14) Inflammatory cytokines have a powerful impact on hypothalamic control of appetite, causing anorexia, activating muscle protein breakdown and inhibiting muscle protein synthesis , and potentially stimulating hypermetabolism. They also indirectly impact nutritional status and muscle by causing insulin resistance, and suppression of anabolic hormone production, such as growth hormone, IGF-1 and androgens (13).

Other factors believed to impact upon risk of malnutrition development in CKD includes impairment of the olfactory system and taste (15;16). Furthermore, polypharmacy has also been found to be a significant risk factor (17). Dialysis is also known to have a catabolic impact by increasing amino acid losses and has been linked to a reduction in appetite in patients on dialysis days (12).

Prevalence and Screening/Assessment

The assessment of malnutrition is well documented in CKD, with varying prevalence depending on screening and assessment modalities. This paper highlights some recent evidence in this regard. Macedo et al, investigated the prevalence of malnutrition (7p-SGA), pre-sarcopenia (low muscle strength or low muscle mass) and sarcopenia (low muscle strength and low muscle mass) in 170 older (> 60 years) HD patients in Brazil ((18). They found that in this group 35.3 were pre-sarcopenic, 14.1 were sarcopenic, and 58.8% were malnourished. Additionally, in the group of patients who had both sarcopenia and malnutrition they had reduced markers of body composition and cellular health (e.g. bioelectrical impedance assessment (BIA) phase angle) and reduced survival.

Kanda et al, investigated the relationship between 'malnutrition inflammation complex' (measured by low serum albumin and high C reactive protein (CRP)) and functional status (measured by the composite of two activities of daily living questionnaires, Katz and Brody) in 5630 HD patients across several countries (19). They found that although prevalence varied there was a strong relationship with those who had a positive malnutrition inflammation complex and low functional status with mortality.

The effects of comorbidities in CKD are another issue to consider with malnutrition risk. A recent Israeli study investigated 375 patients on HD with and without diabetes (20). They found that despite patients with diabetes having a higher BMI, they had a higher malnutrition risk predominantly due to reduced albumin (<38 mmol/L). They also found that CRP was higher numerically in diabetic patients and haemoglobin was significantly lower; and both CRP and haemoglobin predicted malnutrition risk.

Other factors to consider include the relationship between malnutrition and inflammation in CKD and mental function and health. For example, a recent study

showed that the malnutrition inflammation complex score (MIS) was related to higher scores of depression and reduced cognitive function in 132 older adults (> 65 years) with CKD (21). Another study noted reduced health related quality of life scores with malnutrition in dialysis patients (119 HD and 31 PD) (22).

Screening tools

Of note there is a dearth of consensus regarding the use of screening tools in the diagnosis of malnutrition in CKD. It has been long understood that different screening tools will lead to differing prevalence. A recent study compared the use of the GLIM criteria for the assessment of malnutrition compared to 7p-SGA and MIS in HD patients (23). This study had two cohorts of patients (Italy, n=121 and Brazil, n=169). They found that the GLIM criteria had lower 'fair' agreement, sensitivity and accuracy compared to the 7p-SGA and MIS. Furthermore, another research group compared the use of four screening tools (MIS, OSND (objective score of nutrition on dialysis), GNRI (geriatric nutritional risk index) and NRI (nutritional risk index)) against the GLIM criteria (considering it as a 'gold standard') in 318 HD patients (24). They also performed multifrequency BIA measurements and calculated the BIA phase angle, fat free mass (FFM) and skeletal muscle mass (SMM). According to the GLIM criteria, 22.0% had severe malnutrition and 23.9% had moderate malnutrition. Those patients with malnutrition had significantly reduced anthropometric measurements (e.g. BMI; mid upper arm circumference (MUAC) and mid upper arm muscle circumference (MUAMC)); and BIA measurements (e.g. phase angle , fat mass index (FMI), FFM index (FFMI) and SMM index (SMMI)). Plasma albumin was significantly reduced and CRP significantly raised. GNRI was found to be the most sensitive score in identifying malnutrition diagnosed by GLIM criteria, but MIS was more specific and better in predicting the individual components of the GLIM criteria.

In addition, a study by Hassanin et al (2021) (n= 98 HD patients) utilised the PG-SGA as a reference standard and compared with use of the dialysis malnutrition score (DMS) (similar to the PG-SGA but has additional elements on dialysis history and subjective assessment of the loss of muscle and fat mass), and different cut off points for BMI (<23 kg/m^2 (ISRNM) and 18.5 kg/m^2 (ESPEN)) (25). They found that 72.4% were diagnosed as having malnutrition by DMS which was very similar to the PG-SGA (71.4%). Use of BMI alone was not a reliable screening method in this population. Finally, an important recommendation from a recent ESPEN guideline paper is that body composition assessment should be undertaken in the diagnosis of malnutrition (26).

Treatments

Research has identified that restriction of dietary protein may have a positive effect on preserving kidney function and possibly benefiting nutritional status in CKD patients. Studies have highlighted significant effects of low protein diets , shown to reduce proteinuria, metabolic acidosis, improve survival and reduce chances of needing dialysis (or delaying time to dialysis) (27). A recent study highlighted the effects of long term (8 years) dietary protein restriction (n=299 patients with CKD stage 4)) (28). They compared patients on a controlled protein diet (CPD) (0.8 g/kg/day), a low protein diet (0.6 g/kg/day) and unrestricted protein diet (UPD). Those in the CPD and low protein diets groups had preserved BMI and albumin compared to the UPD group. They also showed that survival was significantly different between the groups: UPD - 42.4 %, CPD - 64.1 % and low protein diet - 74.4% at 70 months. Conversely, some studies have shown negative results, such as Hsu et al., 2021, who recruited 73 CKD stages 3-5 patients and asked patients to adopt a low protein diet (target 0.8 g/kg/d) (29). Only 34% of patients managed to adhere to the diet. There were 25 patients on a low protein diet (mean: 0.6+/-0.2 g/kg/d) and 48 on a non-low protein diet (mean: 1.0+/-0.2 g/kg/d). Those on the low protein diet had reduced albumin, haemoglobin, leucine and physical function (6M walking speed test). The mean daily calorie intake was 22 ± 5 kcal/kg/day for the low protein diet group, with only 11 (15%) patients met the recommended daily calorie intake of 30–35 kcal/kg/day. This is an issue for further consideration as it is understood that energy intake is critical for maintaining protein anabolism (e.g. ATP for protein turnover), especially during low protein diet protocols. Therefore, the most important factor is to support healthy dietary changes which are energy sufficient through enhanced nutritional counselling. One Taiwanese study aimed to potentially solve this energy deficiency issue by trialling a low protein diet along with the use of a renal-specific oral nutritional supplement (ONS) (Abbott Suplena®/Nepro LP®) in 35 stage 3b-5 CKD patients (30). After 6 months there were significant improvements in daily calorie intake ($p < 0.001$), body weight ($p < 0.001$) and handgrip strength ($p = 0.036$).

Further to utilisation of a low protein diet, other methods for manipulating the generation of uremic toxins have been suggested, such as supplementation with pre- and pro-biotics. Thereby, manipulating GI tract microbiota and potentially reducing uremic toxin production. A recent study has begun trialling a combined use of a probiotics + low protein diet diet in CKD patients (31). A further small study (n=12) has investigated the use of Inulin in HD patients (32). Unfortunately, in this study there was no effect of Inulin on uremic toxins. More studies with larger participant groups will be needed to confirm or refute this hypothesis.

Treatments specifically targeting the improvement of energy and protein intake have been researched in CKD (e.g. by oral supplementation and dietary/nutritional counselling). Some recent highlights include a study by Sahathevan et al,. which sought to investigate the effects of 6 month treatment with ONS, in addition to standard nutritional counselling (33). They recruited 56 patients on HD with PEW diagnosis. The patients who took ONS received Novasource™ Renal, Nestle which has 475 kcal and 21.7g protein per serving. Patients in the ONS group had improved muscle measurements (by ultrasound) in quadriceps muscle group (p <0.001),

increased dry weight (p = 0.039), mid-thigh girth (p = 0.004), serum prealbumin (p = 0.005), normalized protein catabolic rate (p = 0.025), and dietary intakes (p < 0.001), along with lower malnutrition–inflammation score (MIS) (p = 0.041). Furthermore, the ONS group had a lower PEW prevalence (24% less from baseline).

A recent Swiss multi-centre study highlighted that the response to nutritional support (e.g. ONS and/or enteral nutrition) is better in regards to reducing mortality in those hospitalised patients with reduced eGFR on admission (34). If oral intake and supplementation is not sufficient to meet protein-energy demands, then enteral and parenteral nutrition should be considered for hospitalised patients and this has been recently outlined in an ESPEN guideline paper (26).

Another important consideration includes the incorporation of protein intake around the dialysis time period. Dialysis is a catabolic process which increases losses of amino acids in the dialysate (~15g), stimulates muscle protein breakdown and impairs muscle protein synthesis (causes anabolic resistance) (35)(36). This is complicated further by the issue that many patients are typically older and physically inactive, which further impairs muscle protein synthesis (35). Therefore, it has been suggested that enhancing protein intake around dialysis may have a positive effect. This also may work synergistically with exercise interventions, although more research is needed. A recent study showed that protein ingestion (40 g dose of milk protein concentrate) during HD sessions compensated for the reductions in amino acids (AA) during dialysis (AA removal) (37). They also additionally performed exercise sessions (dialysis cycle ergometer) and showed that exercise did not have a negative effect on reducing plasma AA. A further review article by Hendriks et al, discusses detailed strategies to improve nutritional status in HD patients using protein intake, such as during dialysis (38). A further interesting concept discussed includes the use of pre-sleep protein intake to further encourage muscle protein anabolism during sleep. Mouillot et al, 2021 showed that HD sessions increase the *wanting* and spontaneous intake of protein foods, which correlated with decreases in plasma amino acids (39).

Drug treatments

Specific drug treatments suggested for CKD malnutrition-wasting include growth hormone administration (40). Growth hormone has a potent protein-anabolic effect via directly affecting growth hormone receptors in muscle and indirectly via hepatic IGF-1. Some studies indicate that growth hormone is useful in CKD promoting fat free mass accretion. The research is still underway and needs further exploration. Thyroid hormone supplementation in patients with hypothyroidism may also be beneficial. For example, Deng et al, showed that by correcting hypothyroidism in CKD patients there were noticeable significant improvements in albumin, haemoglobin and handgrip strength (41). Appetite stimulants such as Megestrol Acetate could be a possible treatment as studies have shown use in CKD patients improves appetite, food intake, body weight and serum albumin (12). Other potential agents which may have anabolic and/or anti-catabolic actions in CKD include vitamin D and androgenic anabolic steroids, such as testosterone or nandrolone (42). Myostatin inhibitors (e.g. antibodies), selective androgen receptor modulators

(SARMS) and other drugs such as ghrelin mimetics should be considered for future human clinical trials in CKD (42;12). Figure 1 highlights some of these potential treatment modalities for disease related malnutrition in CKD, discussed in this paper.

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Figure 1. Schematic diagram highlighting potential treatment modalities for DRM in CKD. (+) indicates positive effects, (-) indicates negative effects, (?) indicates unknown at present. First, a low protein diet may be useful in patients not on dialysis in reducing uremic toxin production and improving nutritional status-however, they need to be well planned and sufficient in energy intake. Energy and protein supplementation has positive effects and may also be useful during dialysis in an effort to reduce catabolism and overcome anabolic resistance. Further, exercise may also have beneficial effects e.g. on muscle protein synthesis and be a consideration during dialysis (potential synergy with nutrition-to be confirmed). Manipulation of the gut microbiome with pre-/pre- biotics may also be helpful in reducing uremic toxin production-however, research is still in its infancy in this field. Finally, a range of anabolic and anti-catabolic drugs and medications may have beneficial effects on nutritional status, such as growth hormone (GH) and thyroid hormone (T3/T4).

Key points:

1) Disease related malnutrition “is a complex syndrome resulting from inadequate intake of nutrients that does not fulfil the patient's physiological requirement and from a disease-related systemic inflammatory response”(5)

2) There is a dearth of consensus regarding the use of screening tools in the diagnosis of malnutrition in CKD.

3) Low protein diets which are carefully developed and monitored ensuring sufficient energy intake maybe useful in reducing CKD associated malnutrition, alongside the use of specific supplements such as probiotics.

4) Specific considerations around nutritional supplementation (e.g. protein) and exercise during dialysis in an effort to reduce anabolic resistance and catabolism is an interesting area that requires further research.

5) Further research is required to develop and test the effectiveness of interventions which reflect the multifaceted pathophysiology and impact of disease related malnutrition on chronic kidney disease.

Conclusion

CKD is a rising global health burden. Disease related malnutrition in CKD is common with devastating outcomes. It is therefore vital to prioritise the development of a comprehensive pathway of care including assessment and management strategies that are aimed at improving morbidity and mortality in these patients. To inform such evidence-based healthcare additional research is urgently required in relation to the utility of screening tools such as the GLIM criteria. For example: to determine if disease specific cut offs for important factors such as inflammation are required; and to reach consensus on the most appropriate screening tool(s) for clinical application. In relation to treatment modalities, sufficiently powered studies testing interventions which reflect the complexity of the pathophysiology of disease related malnutrition in CKD, such as multi-modal interventions (43) to aid the development of standardised treatments for these patients is required. The significant morbidity and mortality associated with disease related malnutrition in CKD underscores the importance of progressing this work.

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