REVIEW

OPEN

Dietary protein interventions to improve nutritional status in end-stage renal disease patients undergoing hemodialysis

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Purpose of review

Poor nutritional status is prevalent among end-stage renal disease patients undergoing hemodialysis. Chronic hemodialysis patients show an accelerated decline in skeletal muscle mass and strength, which is associated with higher mortality rates and a reduced quality of life. The current review aims to summarize recent advances regarding underlying causes of muscle loss and interventions that support muscle mass maintenance in patients with chronic hemodialysis.

Recent findings

Muscle maintenance in chronic hemodialysis patients is compromised by low dietary protein intake levels, anabolic resistance of skeletal muscle tissue, sedentary behavior, and amino acid removal during hemodialysis. Studies assessing the effect of increased protein intake on nutritional status generally show beneficial results, especially in hypoalbuminemic chronic hemodialysis patients. The muscle protein synthetic response following protein ingestion in chronic hemodialysis patients may be enhanced through incorporation of structured physical activity and/or concurrent ketoacid ingestion.

Summary

A coordinated program that combines nutritional and physical activity interventions is likely required to attenuate the decline in muscle mass and strength of chronic hemodialysis patients. Nephrologists, dieticians, and exercise specialists should collaborate closely to establish guidelines regarding the appropriate quantity and timing of protein ingestion. In addition, they should provide tailored nutritional and physical activity interventions for chronic hemodialysis patients (see video, Supplemental Digital Content 1, Video abstract, http://links.lww.com/COCN/A14).

Keywords

kidney disease, muscle wasting, nutrition, physical activity, protein

INTRODUCTION

Poor nutritional status is frequently observed in all stages of chronic kidney disease (CKD), but its prevalence increases with advanced stages [1]. In patients with end-stage renal disease (ESRD), the glomerular filtration rate is below 15 ml/min/1.73 m^2 and metabolic waste products are insufficiently excreted from the body. Waste products can accumulate to lethal concentrations in ESRD and should be removed from the body through the use of renal replacement strategies.

Hemodialysis is globally the most applied chronic renal replacement strategy when kidney transplantation is not possible. However, after initiation of chronic hemodialysis (CHD) therapy, the rate of loss of skeletal muscle mass and strength is high and impairments in physical function become a common observation [2,3]. A recent meta-analysis by Carrero *et al.* [4▪] reported that protein-energy wasting, a syndrome characterized by the progressive loss of body protein and energy stores (i.e. muscle

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KEY POINTS

- Low levels of habitual dietary protein intake and physical activity, anabolic resistance of skeletal muscle tissue, and nutrient loss during hemodialysis are key causes of poor nutritional status among patients with chronic hemodialysis.
- Protein-rich foods/supplements can be applied to increase dietary protein intake levels and improve nutritional status in patients with chronic hemodialysis, achieving the greatest impact in those patients with the poorest baseline nutritional status.
- Anabolic resistance of skeletal muscle tissue in patients with chronic hemodialysis may be overcome through ingesting well over 20 g high-quality protein per meal or concurrent ingestion of essential amino acids/ketoacids with lower protein amounts.
- Implementing structured physical activity in the daily routine of patients with chronic hemodialysis will be instrumental to alleviate anabolic resistance, and, as such, support skeletal muscle maintenance.
- Tailored nutritional care, including protein ingestion during dialysis for hemodynamic stable patients, should be provided throughout dialysis days to compensate for amino acid removal during hemodialysis.

and fat mass), is present in 28–54% of CHD patients.

Skeletal muscle mass is regulated by a dynamic balance between the continuous synthesis and breakdown of muscle proteins. The skeletal muscle protein pool possesses a turnover rate of 1–2% per day, which results in quick adaptation of muscle tissue to circumstances (e.g. muscle atrophy following disuse) [5]. Loss of skeletal muscle mass can be attributed both to a decrease in muscle protein synthesis, as well as to an increase in muscle protein breakdown rates. It is suggested that catabolic pathways in patients with ESRD are upregulated because of disease-related complications, such as insulin resistance and accumulation of metabolic waste products [3]. To support muscle maintenance in those patients, anabolic interventions to induce an equivalent increase in muscle protein synthesis rates should be implemented in clinical care. Two key anabolic strategies essential for muscle maintenance are protein ingestion and physical activity.

Therefore, the purpose of the current review is to describe the impact of dietary protein interventions with and without physical activity on the nutritional status of ESRD patients undergoing hemodialysis as demonstrated in recent literature.

DIETARY PROTEIN INTAKE

Protein ingestion is required to maintain skeletal muscle mass. Dietary protein is digested and amino acids are absorbed in the gut, with ~50% of the dietary protein-derived amino acids being subsequently released into the circulation over a 5-h postprandial period [6]. Amino acids that become available in the circulation can serve as precursors for de-novo muscle protein synthesis [7]. However, amino acids are more than just building blocks for muscle protein synthesis, as they also function as signaling molecules. Essential amino acids, and leucine in particular, have the ability to stimulate the mammalian target of rapamycin complex 1 (mTORC1) activity, thereby increasing anabolic signaling [8]. As shown in Fig. 1A, ample protein ingestion and subsequent hyperaminoacidemia increases muscle protein synthesis rates and inhibits muscle protein breakdown rates, allowing net muscle protein accretion during the postprandial period [9].

Habitual dietary protein intake

In healthy young adults, ingestion of 20 g high-quality protein has been shown to maximize postprandial muscle protein synthesis rates [10]. In older adults, the muscle protein synthetic response following such an amount of protein ingestion is attenuated when compared with younger adults, a phenomenon that has been coined anabolic resistance [11]. Recently, van Vliet *et al.* [12▪▪] reported that in CHD patients, ingestion of a mixed-meal containing 20 g intrinsically labeled protein on a nondialysis day failed to increase skeletal muscle protein synthesis rates. In addition, less protein-derived amino acids were released into the circulation following meal ingestion ($41 \pm 5\%$ in CHD patients vs. $61 \pm 4\%$ in control subjects). Together, this suggests that CHD patients show anabolic resistance to protein ingestion.

In healthy young adults, a daily protein intake of 0.8 g/kg body weight is generally considered sufficient to achieve a net balance between muscle protein synthesis and breakdown rates. Because of anabolic resistance of skeletal muscle tissue and the upregulation of catabolic pathways in CHD patients, a higher protein intake level may be required to maintain muscle mass. Current clinical guidelines recommend CHD patients to ingest 1.2 g protein/kg body weight/day [13]. CHD patients often struggle to follow such dietary recommendations because of time constraints on dialysis days, altered taste, and early satiety [14–16]. Consequently, many CHD patients ingest less protein than recommended, with recent studies reporting

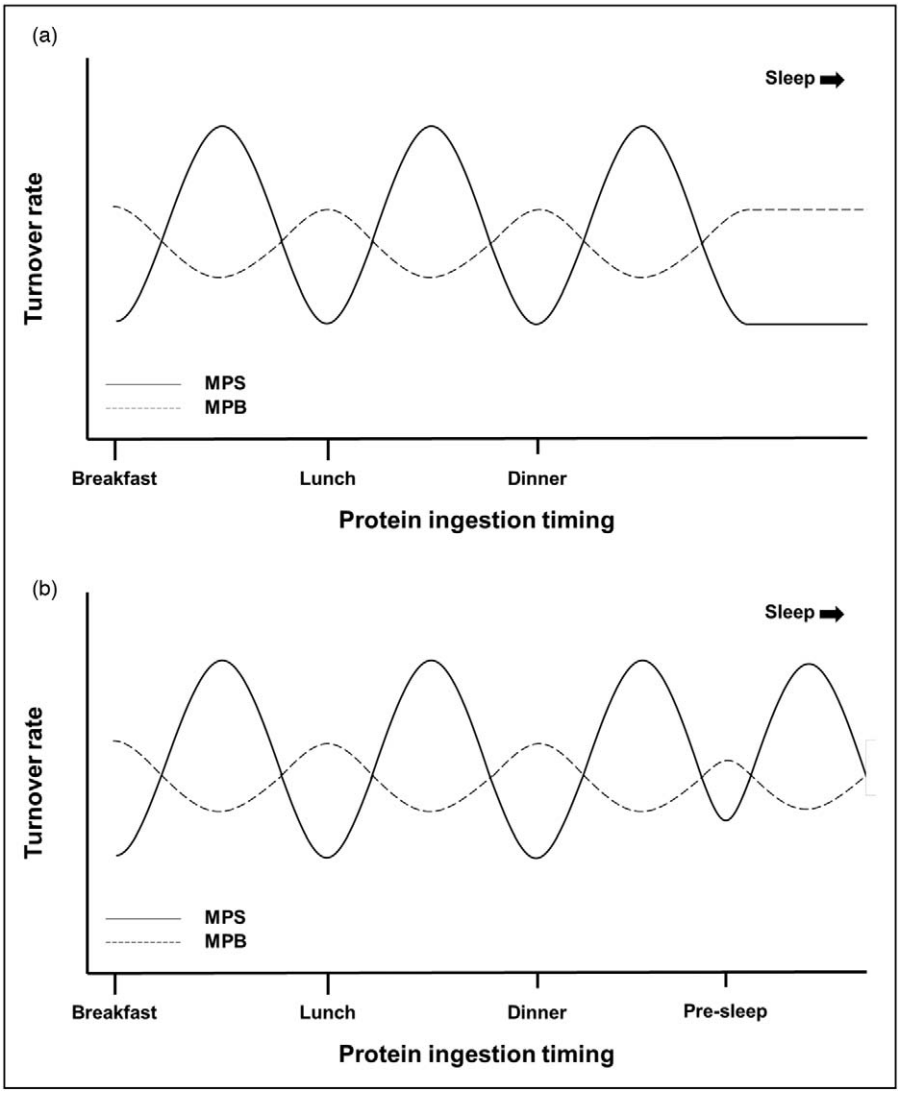

FIGURE 1. Effect of ingesting protein at (a) three moments and (b) four moments including presleep on muscle protein synthesis and breakdown rates throughout the day. In the postabsorptive state, muscle protein breakdown rates exceed synthesis rates. Following protein ingestion, muscle protein synthesis rates increase while breakdown rates decrease, allowing net muscle accretion during the postprandial period. Ingestion of ample protein prior to sleep can increase overnight muscle protein synthesis rates and lower proteolysis. MPB, muscle protein breakdown; MPS, muscle protein synthesis.

a protein intake below 1.0 g/kg body weight/day in ~50% of ESRD patients undergoing hemodialysis [17–20]. As low protein intake is associated with loss of muscle mass in patients with advanced stage CKD [21,22], dietary (protein) intake of CHD patients, especially those at high risk of malnutrition, should be monitored closely.

Protein and/or amino acid supplementation

Nutritional interventions should be started when CHD patients have a habitual protein intake below 1.0 g/kg body weight/day or energy intake below 30 kcal/kg body weight/day [13]. Ideally, a renal dietician should provide nutritional counseling after initiation of CHD therapy [23]. According to current guidelines, nutritional counseling should aim to achieve a dietary intake of 1.2 g protein and 30–35 kcal/kg body weight/day in patients at risk of malnutrition [13]. This can be achieved through increased intake of normal foods, food fortification, and/or the provision of oral nutritional supplements. Furthermore, each meal should contain ample protein to induce a postprandial increase in skeletal muscle protein synthesis and inhibit muscle protein breakdown. Considering the

anabolic resistance of skeletal muscle tissue in CHD patients [12▪▪], patients likely need to ingest well above 20 g high-quality protein to allow a proper muscle protein synthetic response.

In healthy older adults, it has been shown that due to anabolic resistance ingestion of ~35 g protein is required to maximize postprandial muscle protein synthesis rates [11]. Yet, in CHD patients, the ingestion of such large amounts of protein would also represent a high phosphate intake. This is undesirable in patients with ESRD because their renal excretion of phosphate is compromised and hemodialysis usually is ineffective to normalize serum phosphate concentrations [18]. Dietary phosphate intake is, therefore, an important contributor to hyperphosphatemia in CHD patients, which is associated with a greater prevalence of cardiovascular disease [24]. Because phosphate absorption from plant-based proteins is lower than from animal-based proteins, it has been suggested that increasing the percentage of dietary protein derived from plant-based protein sources may reduce hyperphosphatemia in CHD patients [24,25,26▪]. However, plant-based protein sources generally have lower (essential) amino acid contents and a specific lack of lysine and/or methionine compared to animal-based (high-quality) protein sources [27,28▪]. The latter may be compensated for by ingesting a combination of several plant-based protein sources. Nonetheless, the lower essential amino acid contents, and the low leucine content in particular, of plant-based protein sources may further increase the amount of protein required to induce a proper muscle protein synthetic response in CHD patients [28▪].

The use of essential amino acid fortification may provide an option to induce a muscle protein synthetic response in CHD patients with less phosphate intake. Our laboratory has shown in healthy older adults that ingestion of 15 g milk protein together with 1.5 g free leucine induces a greater postprandial muscle protein synthetic response than the ingestion of 15 g milk protein only [8]. More recently, we showed that the ingestion of 6 g branched-chain ketoacids can induce a postprandial anabolic response in healthy older adults [29▪]. Ketoacids are precursors of corresponding amino acids and can be utilized for de-novo muscle protein synthesis without providing any nitrogen, and, as such, would not add to uremic toxin accumulation [30]. However, it should be noted that Li *et al.* [19] recently reported no benefits of 6 months ketoacid supplementation on the nutritional status of Chinese CHD patients. Future studies that assess the muscle anabolic response following ketoacid ingestion in CHD patients should be conducted to assess whether it could help to support muscle maintenance.

Oral nutritional supplements

Specific oral nutritional supplements have been developed for CHD patients. These products typically have a higher energy and protein density and lower phosphate, potassium, and sodium contents when compared to other nutritional supplements for clinically compromised patient groups [13]. CHD patients receiving such supplements twice daily for a period of 3 months showed improvements in postabsorptive plasma amino acid profiles and serum (pre)albumin concentrations, a surrogate measurement often used to estimate nutritional status of dialysis patients [31]. However, no changes in lean body mass were observed over the study period. This indicates that the provided supplements (containing 9.4 g protein) were not able to induce net muscle protein accretion, which is at least partly attributed because of the anabolic resistance in the CHD population. A recent meta-analysis showed that though short term ($\leq$3 months) oral nutritional supplementation increases body mass index and serum albumin concentrations in CHD patients, prolonged (>3 months) supplementation does not necessarily show such benefits [32▪]. These contradictory results may be due the low compliance and adherence to oral nutritional supplementation often observed in CHD patients. To achieve long-term compliance in CHD patients, protein supplements should be easy to prepare, convenient to consume, and have an acceptable taste. Consequently, the use of more protein dense meals and healthy food products may represent a more practical means to increase long-term daily protein consumption. The use of nonprotein supplements, such as creatine and omega-3 fatty acids, to support muscle maintenance has recently been described in detail [33].

Timing of oral nutritional supplement ingestion may also influence its efficiency to stimulate muscle protein synthesis and, as such, to support muscle maintenance. Ingestion of high-protein liquids induce satiety and may reduce energy intake during a subsequent meal [34]. Recently, protein ingestion before sleep has been introduced as an additional (meal) moment to augment daily protein consumption in populations with low protein intake [35]. Presleep ingestion of 40 g casein has been shown to have no effect on appetite and energy intake the next morning in older adults [36]. Furthermore, protein ingested before sleep has been shown to be properly digested and absorbed, thereby increasing overnight muscle protein synthesis rates (Fig. 1B). However, the impact of ingesting a protein-rich supplement/snack prior to sleep on dietary protein intake and nutritional status in CHD patients remains to be determined.

PHYSICAL ACTIVITY TO AUGMENT POST-PRANDIAL MUSCLE PROTEIN SYNTHESIS

In addition to protein ingestion, physical activity is essential for muscle maintenance. Current guidelines recommend CHD patients without contraindications to perform at least 150 min of moderate-intensity physical activity per week [37]. Regrettably, CHD patients typically have a sedentary lifestyle and often fail to meet these guidelines [38]. This low level of habitual physical activity represents the key factor responsible for the development of anabolic resistance in CHD patients. Physical inactivity has been shown to induce anabolic resistance of skeletal muscle tissue [39▪] and is related to lower physical functioning in CHD patients [40]. Therefore, ample physical activity is likely required to achieve the full anabolic potential of dietary protein. A single bout of physical activity can increase the sensitivity of skeletal muscle tissue to the anabolic effects of protein ingestion for a period up to 24 h [41]. Although aerobic exercise has been shown to increase aerobic capacity in CHD patients [42], resistance-type exercise is considered to be the most potent form of physical activity to increase muscle mass and strength [43]. Nevertheless, a recent study by Sheshadri *et al.* [44▪] reported that low-intensity exercise (i.e. walking) already resulted in improved muscle mass maintenance in CHD patients. Structured and sustained physical activity interventions can be applied to alleviate anabolic resistance and, as such, will likely further complement and augment the effects of dietary protein intervention. Therefore, CHD patients should be counseled to incorporate more habitual physical activity and structured exercise training in their daily living routines. However, because of the high prevalence of exercise intolerance and low adherence and compliance to physical activity interventions in the CHD population [45], more effective exercise programs will need to be developed.

INTERVENTIONS DURING HEMODIALYSIS SESSIONS

ESRD patients typically undergo two to three hemodialysis sessions per week, each lasting ~4 h. These hemodialysis sessions represent a unique situation of compromised food intake and physical activity. During hemodialysis, patients sit in a lounge chair or lie in bed and typically stay sedentary for the entire procedure. In dialysis departments not providing in-center meals, food intake during hemodialysis is generally low because of restrictive eating policies, disrupted meal schedules, and/or inconvenience of bringing foods from home [46]. Furthermore, hemodialysis activates an inflammatory cascade and removes small-sized nutrients, such as amino acids, along with metabolic waste products through the semipermeable dialysis membrane. Recently, we have shown that during a single hemodialysis session approximately 12 g amino acids are removed from the circulation, which would be equivalent to the amount of amino acids that is released into the circulation following the ingestion of a typical meal containing ~25 g protein [47▪]. As a consequence, plasma amino acids decline by ~20% despite the average consumption of ~20 g protein during hemodialysis. Pupim *et al.* [48] previously showed that the decline in circulating amino acid concentrations during hemodialysis induces a negative net forearm amino acid balance, indicative of increased skeletal muscle proteolysis. As depicted in Fig. 2A, such a catabolic state may endure for at least 2 h after the end of a hemodialysis session in fasted patients [48]. To support muscle maintenance during hemodialysis, amino acid removal should be (at least) compensated for through protein administration.

Protein intake during hemodialysis

Protein-rich meals, snacks, or oral nutritional supplements during hemodialysis are suggested to increase dietary protein intake on dialysis days, and can be used to improve nutritional status and survival rates of CHD patients [49▪]. Muscle catabolism during hemodialysis may be prevented, or even reverted into anabolism, through ingestion of ample high-quality protein (Fig. 2B). Ingestion of ~60 g protein during hemodialysis has been shown to prevent the decline in circulating amino acid concentrations and induce a positive forearm amino acid balance throughout hemodialysis [48,50]. However, protein ingestion during hemodialysis will also be accompanied by greater amino acid removal [47▪]. Also considering the presence of anabolic resistance, CHD patients likely need to ingest well above 30 g protein during hemodialysis to allow increased muscle protein synthesis rates. Ingestion of a lower amount of protein may not increase muscle protein synthesis rates but could attenuate muscle proteolysis and, as such, improve net protein balance during hemodialysis [50]. Yet, the optimal amount of protein that should be ingested during hemodialysis to support muscle maintenance remains to be determined.

Many studies have reported benefits of providing various amounts of protein-rich nutrition during hemodialysis. Benner *et al.* [51] performed a retrospective evaluation of a pilot program and found that oral nutritional supplementation during hemodialysis, providing 16 or 22 g protein, reduced mortality rates in hypoalbuminemic CHD patients.

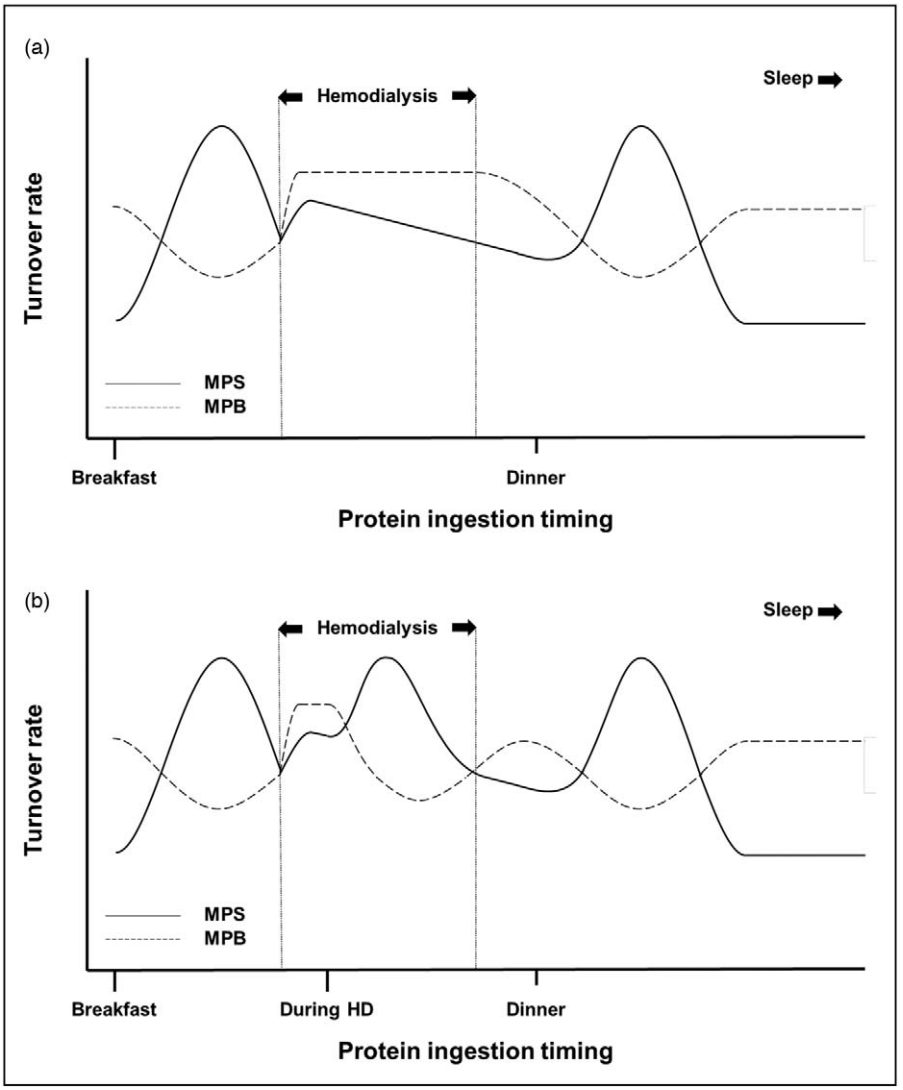

FIGURE 2. Effect of (a) no protein ingestion and (b) protein ingestion during hemodialysis on muscle protein synthesis and breakdown rates throughout the day. Because of amino acid removal during hemodialysis, muscle protein breakdown rates increase and exceed synthesis rates. In fasted patients, this catabolic period continues even after the end of the hemodialysis session. Ingestion of ample protein during hemodialysis stimulates muscle protein synthesis rates and inhibits breakdown rates, allowing net muscle accretion. MPB, muscle protein breakdown; MPS, muscle protein synthesis.

More recently, it has been reported that hypoalbuminemic CHD patients who ingested a small meal (200 mL milk with 2 egg whites; providing 14 g protein) every hemodialysis session showed a greater increase in serum albumin levels after 3 months than control subjects receiving nutritional counseling [52]. In support of these positive findings, it has been reported that providing oral nutritional supplements, containing 14–20 g protein, during hemodialysis after hospitalization of hypoalbuminemic CHD patients reduced readmission rates [53]. Thus, it seems likely that malnourished/hypoalbuminemic CHD patients benefit from protein ingestion during hemodialysis. However, the impact of protein ingestion during hemodialysis in better nourished patients is still a matter of debate, probably because the benefits are less distinct. Jeong *et al.* [54▪▪] recently performed a large randomized controlled trial to assess the effect of protein supplementation during hemodialysis on physical functioning in CHD patients with normal (~4 g/dl) serum albumin levels. Though gait speed was increased after 6 and 12 months of supplementation, no effects on body composition were shown. This suggests that simply providing a protein supplement during hemodialysis is not sufficient to improve muscle mass in well nourished CHD patients. Thus, more research to identify effective nutritional strategies during hemodialysis to prevent muscle loss in CHD patients is still required.

Dietary protein intake during hemodialysis is presently not implemented in clinical guidelines, as some nephrologists are concerned about patient safety and increased staff burden [55]. Dialysis departments in Europe and Asia are more likely to allow food ingestion during hemodialysis compared to dialysis departments in North America [56]. One of the most frequently cited concerns regarding food intake during hemodialysis is the postprandial decrease in systemic blood pressure, which occurs because of increased perfusion of the splanchnic region following food ingestion [55,57▪]. Though the postprandial drop in blood pressure is amplified during hemodialysis [57▪], Choi *et al.* [58] reported no effect of high-protein meals on the frequency of symptomatic hypotensive events. Patients' hemodynamic stability, meal composition, and meal timing may influence the postprandial drop in blood pressure. In patients who do not tolerate food intake during hemodialysis , intradialytic parenteral nutrition may be used to prevent hemodialysis-related catabolism [59]. In addition, Deleaval *et al.* [60] recently showed that branched-chain amino acids can be provided during hemodialysis by adding them to the dialysate. We would advocate dialysis departments not to restrict eating *per se*, but to apply patient-tailored nutritional care during hemodialysis combined with nutritional counseling to improve habitual dietary intake between hemodialysis sessions.

Exercise during hemodialysis

In addition to nutritional interventions, physical activity interventions can also be implemented during hemodialysis sessions to prevent the loss of muscle mass and strength (Fig. 3). Exercise during hemodialysis can induce (moderate) improvements in physical functioning, muscle strength, and quality of life [43,54▪▪,61]. It also represents an opportunity to counsel patients on physical activity in their daily living. In patients who are not able to exercise during hemodialysis, neuromuscular electrical stimulation could be employed to activate skeletal muscles, thereby increasing muscle strength and physical functioning [62]. However, studies that

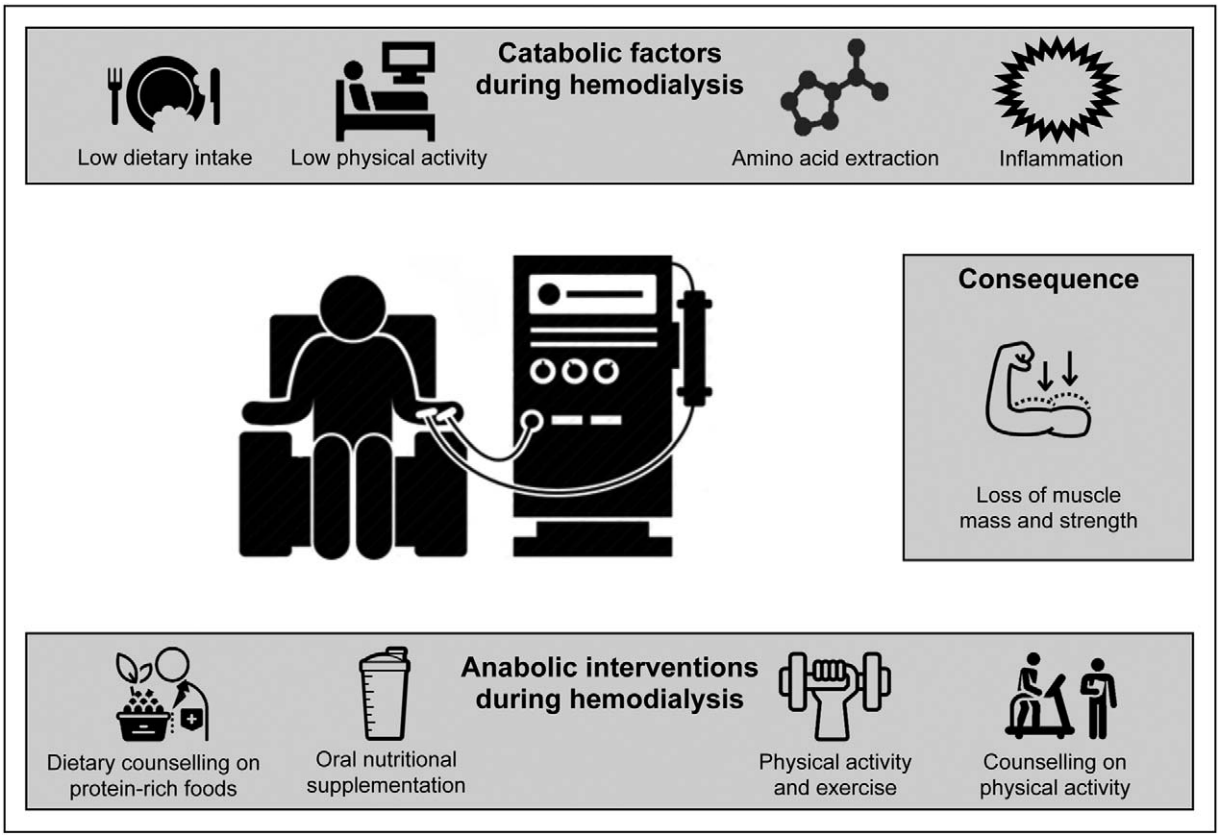

FIGURE 3. Overview of catabolic factors during hemodialysis and anabolic interventions that may be applied during this period. During a hemodialysis session, patients typically have low levels of dietary intake and physical activity, while the procedure removes amino acids from their circulation and activates an inflammatory cascade. This results in a catabolic period during hemodialysis, which promotes the loss of muscle mass and strength. Interventions to support muscle maintenance that can be applied during hemodialysis include dietary counseling to improve habitual dietary intake, providing protein-rich foods, prescribing physical activity, and counseling to increase habitual physical activity levels.

apply (resistance-type) exercise training prior to or during hemodialysis generally fail to show increases in muscle mass [43]. Exercise during hemodialysis is performed in a period of reduced circulating amino acid availability. This may prevent an anabolic response following exercise and, as such, prevent net muscle accretion over time. In addition, a greater blood flow to exercising muscles during this period of reduced amino acid availability may actually lead to increased muscle proteolysis. Therefore, protein ingestion, and the subsequent postprandial hyperaminoacidemia, may be required throughout and after exercise during hemodialysis to achieve a positive net muscle protein balance. We advocate that exercise during hemodialysis should be combined with sufficient protein ingestion to allow a postexercise increase in muscle protein synthesis rates and to inhibit proteolysis. This strategy may also lower the amount of protein required to induce a muscle protein synthetic response, as the performance of exercise prior to hemodialysis has been shown to make the muscle more sensitive to the anabolic properties of subsequent protein ingestion [63]. Though the combination of exercise and nutrition during hemodialysis is likely preferred, future research is needed to assess their synergy and establish nutritional and exercise guidelines for effective implementation during hemodialysis.

CONCLUSION

Poor nutritional status is common among CHD patients because of low protein intake and physical inactivity, anabolic resistance of skeletal muscle tissue, and amino acid removal during hemodialysis. Patient-tailored dietary interventions should aim to increase habitual protein intake levels and induce a muscle protein synthetic response with every meal through ingestion of ample high-quality protein with or without essential amino acid/ketoacid fortification. Implementing structured supervised exercise in the daily routine of CHD patients will enhance the muscle protein synthetic response to protein ingestion. A combination of more physical activity or exercise training with nutritional interventions during hemodialysis will further augment the capacity to maintain or even increase muscle mass. Nephrologists, dieticians, and exercise specialists should collaborate to develop patient-specific lifestyle programs to prevent the loss of skeletal muscle mass in CHD patients.

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Conflicts of interest

F.K. Hendriks, J.P. Kooman, and L.J.C. van Loon have no conflicts of interest.

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