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Malnutrition at the Time of Dialysis Initiation and Indicators of Poor Nutritional Status

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Abstract: Background: The decision to start dialysis for an ESKD patient varies across countries and is influenced by the local nephrology practice, healthcare policies, and cost for dialysis treatment. The Dialysis Outcomes and Practice Patterns Study (DOPPS) Phase 2 with 12 participating countries indicated a greater mortality rate in patients new to dialysis compared to prevalent dialysis patients. Early mortality at the time of dialysis initiation prevails with increased risk up to 80% within the first two months of HD initiation. Apart from catheter vascular access and pre-dialysis care, nutritional status is considered a potentially modifiable risk factor in early mortality. Clearly, pre-existing malnutrition originates from progressive CKD stages 3 to 5 with vulnerability of the patient starting from the point of metabolic derangements associated with falling glomerular filtration rate, late nephrology access, and insufficient pre-dialysis dietetic care during this period. Dialysis treatment is expected to improve nutritional status for patients with a more liberal protein prescription compared to the pre-dialysis stage. However, dialysis treatment is cited to contribute to malnutrition burden, and newly dialyzing patients are at risk of the early mortality attributed to malnutrition as evidenced by diagnostic assessment of nutrition risk screening using SGA, low body mass index (BMI), low mid-arm muscle circumference (MAMC), low albumin, low cholesterol levels, and reduced food intake.

Keywords: Malnutrition, Dialysis, Nutritional Status

Introduction

The term renal failure (R) denotes the inability of the kidneys to perform excretory function leading to retention of nitrogenous waste products from the blood. Functions of the kidney are as follows:

- Electrolyte and volume regulation.
- Excretion of nitrogenous waste.
- Elimination of exogenous molecules, for example, many drugs.
- Synthesis of a variety of hormones, for example, erythropoietin.
- Metabolism of low molecular weight proteins, for example, insulin.
- Acute and chronic renal failure are the two kinds of kidney failure ***(1).***

Classification of RF:

- Acute Renal Failure (ARF):

ARF is the syndrome in which glomerular filtration declines abruptly (hours to days) and is usually reversible. According to the KDIGO criteria, AKI can be diagnosed with any one of the following: (1) creatinine increases of 0.3 mg/dL in 48 hours, (2) creatinine increases to 1.5 times baseline within last 7 days, or (3) urine volume less than 0.5 mL/kg per hour for 6 hours. Recently the term acute kidney injury (AKI) has replaced ARF because AKI denotes the entire clinical spectrum from a mild increase in serum creatinine to overt renal failure ***(2).***

Chronic Renal Failure (CRF):

CRF or chronic kidney disease (CKD) is defined as a persistent impairment of kidney function, in other words, abnormally elevated serum creatinine for more than 3 months or calculated glomerular filtration rate (GFR) less than 60 ml per minute / 1.73m^2. It often involves a progressive loss of kidney function necessitating renal replacement therapy (dialysis or transplantation). When a patient needs renal replacement therapy, the condition is called end-stage renal disease (ESRD) ***(3).***

CKD classified based on grade:

- Grade 1: GFR greater than 90.
- Grade 2: 60 to 89.
- Grade 3a: 45 to 59.
- Grade 3b: 30 to 44.
- Grade 4: 15 to 29.
- Grade 5: Less than 15 ***(4).***

CKD classified based on stage:

- Stage 1: GFR greater than 90.
- Stage 2: 60 to 89.
- Stage 3: 30 to 59.
- Stage 4: 15 to 29.
- Stage 5: Less than 15***(2).***

Renal failure pathophysiology can be described by a sequence of events that happen while during acute insult in the setting of acute renal failure and also gradually over a period in cases of chronic kidney diseases ***(1).***

Treatment / Management:

Treatment options for renal failure vary widely and depend on the cause of failure. Broadly options are divided into two groups: treating the cause of renal failure in acute states versus replacing the renal function in acute or chronic situations and chronic conditions. Below is the summary of renal failure treatment ***(5).***

Acute Renal Failure:

- Mainstay is treating the underlying cause and associated complications.
- In case of oliguria and no volume, overload is noted, a fluid challenge may be appropriate with diligent monitoring for volume overload.

- In the case of hyperkalemia with ECG changes, IV calcium, sodium bicarbonate, and glucose with insulin should be given.
- Oliguric patients should have a fluid restriction of 400 mL + the previous day's urine output (unless there are signs of volume depletion or overload).
- If acidosis: Serum bicarbonate intravenous or per oral, versus emergency/urgent dialysis based on the clinical situation.
- If obstructive etiology present treat accordingly and or if bladder outlet obstruction secondary to prostatic hypertrophy may benefit from Flomax or other selective alpha-blockers ***(3).***
  - *General Measures:*
- First things first, always review the drug list.
- Stop nephrotoxic drugs and renally adjust others. Many supplements not approved by the FDA can be nephrotoxic.
- Always record ins and outs.
- Monitor daily weights.
- Watch for complications, including hyperkalemia, pulmonary edema, and acidosis-all potential reasons to start dialysis.
- Ensure good cardiac output and subsequent renal blood flow.
- Pay attention to diet: total caloric intake should be 35 to 50 kcal/kg per day to avoid catabolism. Potassium intake restricted to 40 mEq per day; phosphorus restricted to 800 mg per day. If it becomes high, treat with calcium carbonate or other phosphate binder. Magnesium compounds should be avoided.
- Treat infections aggressively ***(4).***
  - *Immediate Dialysis Indications:*
- Severe hyperkalemia.
- Acidosis.
- Volume overload refractory to conservative therapy.
- Uremic pericarditis.
- Encephalopathy.
- Alcohol and drug intoxications ***(6).***

Chronic Renal Failure:

- Optimize control of specific causes of CKD such as diabetes mellitus and hypertension.
- Measure sequentially and plot the rate of decline in GFR in all patients.
- Any acceleration in the rate of decline should prompt a search for superimposed acute or subacute process that may be reversible.
- Rule out extracellular fluid volume depletion, uncontrolled hypertension, urinary tract infection, new obstructive uropathy, exposure to nephrotoxic agents (such as NSAIDs or contrast dye), reactivation or flare of the original disease such as lupus or vasculitis.
- Interventions to slow the progression of CKD.
- Reduce intra-glomerular filtration.
- Reduce proteinuria; effective meds include ACE/ARB.
- Strict glycemic control.
- Prevent and treat complications of CKD.
- Discuss renal replacement therapy with patients appropriately and timely.
- Periodically review medications and avoid nephrotoxic medicines. Dose renally excreted medications appropriately.
- Patients with CKD should be referred to a nephrologist when eGFR is less than 30 ml per minute, as this provides enough time for adequate preparation for kidney replacement therapy (***1).***

Golden keys during the management:

- The typical FeNa values for each type of AKI: Pre-renal: Less than 1%; Intrinsic renal greater than 2%; Post-renal: Greater than 4%.
- The typical BUN/creatinine ratios for each type of AKI: Pre-renal greater than 20:1; Intrinsic renal Less than 10:1; Post-renal or normal 10 to 20:1.
- Patients who get diuretics may have a higher urinary concentration of sodium due to the diuretic, falsely elevating the fractional excretion of sodium. In these patients, use the fractional excretion of urea (FeUrea) instead since it is relatively unaffected by diuretics.
- Serum creatinine used as a marker of kidney function is affected by muscle mass (lower muscle mass = falsely low serum creatinine).
- The Modification of Diet in Renal Disease (MDRD) formula includes age, gender, race, BUN, creatinine, and albumin. These are all important factors in measuring kidney function (GFR) and all automatically printed in lab reports.
- Prevention of AKI begins before hospitalization by obtaining a nephrology consultation appropriately in patients with CKD 3, CKD 4, and CKD 5.
- Adjust doses of medications according to estimated glomerular filtration rate (GFR).
- Watch for hyperkalemia while taking simultaneous ACEI or ARB/spironolactone in patients with CKD.
- Check for bone mineral disorders in patients with CKD ***(2).***

Enhancing Healthcare Team Outcomes:

The management of kidney failure is usually done with an interprofessional team of healthcare professionals dedicated to preserving renal function. Kidney failure has enormous morbidity and mortality, costing the healthcare system billions of dollars each year. Today most hospitals have a kidney failure nurse whose job is to educate patients on the causes, detection, and prevention of kidney failure. The pharmacist also needs to regularly audit patient medications for those that are nephrotoxic ***(3).***

These patients should have close follow up to ensure that the renal function is not deteriorating. Finally, the patient needs to be given advice on healthy eating, exercise, discontinuing tobacco and abstaining from alcohol. Kidney disease is not well managed can lead to complete renal failure, which requires dialysis. (level V) Only through open communication between the team members can the morbidity and mortality of renal failure be lowered ***(4).***

Outcomes:

Recovery from acute renal failure depends on the cause of the disease. If the cause is reversible, the prognosis is good and leans toward a full recovery. Partial recovery of renal function may occur if the injury does not fully resolve. Severe cases of acute renal failure can result in death. The prognosis for hospitalized patients with AKI depends largely on the site (ICU or floor) ***(7).***

The mortality rate of patients with AKI on a ventilator is about 80%. AKI patients are at increased risk for progressing into CKD during their lifetime. CKD is correlated with high morbidity and mortality. Cardiovascular mortality is 10 to 30 times higher in ESRD patients treated with dialysis compared to those in the general population (Level V) ***(1).***

Malnutrition in RF and correlation with outcome (death or comorbidity)

Background:

The last three decades witnessed considerable growth in the global burden of chronic kidney disease (CKD), accounted for by 77.5% of end-stage kidney disease (ESKD) patients on kidney replacement therapy (KRT), with 43.1% alone provided by dialysis. Hemodialysis (HD) forms 89% of the global treatment for ESKD patients ***(8).***

The technological delivery of HD treatment to patients today is considered optimal as per medical guidelines for practice with regard to biocompatibility of dialyzer membranes, dialysis dose, frequency of dialyzer reuse,

and duration of dialysis. A significant problem faced by this patient group, however, is malnutrition with a global prevalence of 28–54%, facing a greater risk of mortality, varying from a likelihood of 1.61 to 4.08 ***(9).***
Morbidity arising from malnutrition in these patients severely affects quality of life (QoL), frailty, and increased risk of infections and mortality. Malnutrition in patients on dialysis develops along different pathways from that observed in acute cases of hospitalization and critical illness. Its inception evolves from the early progressive nature of CKD itself, the implementation of a low protein diet to limit CKD progress, and the prolonged period of potentially lifesaving dialysis treatment for patients reaching ESKD ***(10).***
HD treatment itself in terms of dialysis-induced nutrient losses, multiple dialyzer reuse, dialysis-induced inflammation, efficacy of uremia and metabolic acidosis correction, and dialysis adequacy, frequency, and duration are inevitable iatrogenic factors contributing to malnutrition. Concurrently, prevailing non-iatrogenic factors such as suboptimal dietary intakes, taste alterations, poor appetite, insulin resistance, and psychosocial factors are also incriminated in the etiology of malnutrition ***(11).***
Malnutrition occurrence in the dialysis population has generated much research. However, different definition terms exist for malnutrition such as protein-energy wasting, protein-energy malnutrition, malnutrition–inflammation complex syndrome, malnutrition–inflammation–atherosclerosis and uremic wasting syndrome depending on involvement of inflammation, hypercatabolism, and increased uremia ***(12).***
Multiple factors are cited within the etiology of these descriptive malnutrition terms, and implication of some but not all these factors differentially indicates that there is no uniformity in the diagnosis of malnutrition. Comorbidities such as heart failure (left-ventricular failure) and CKD-mineral bone disorder have a bidirectional association with nutritional status ***(13).***

Development of Malnutrition at the Time of HD Initiation and Indicators of Poor Nutritional Status:

The decision to start dialysis for an ESKD patient varies across countries and is influenced by the local nephrology practice, healthcare policies, and cost for dialysis treatment. The Dialysis Outcomes and Practice Patterns Study (DOPPS) Phase 2 with 12 participating countries indicated a greater mortality rate in patients new to dialysis compared to prevalent dialysis patients ***(14).***
Early mortality at the time of dialysis initiation prevails with increased risk up to 80% within the first two months of HD initiation. Apart from catheter vascular access and pre-dialysis care, nutritional status is considered a potentially modifiable risk factor in early mortality. Clearly, pre-existing malnutrition originates from progressive CKD stages 3 to 5 with vulnerability of the patient starting from the point of metabolic derangements associated with falling glomerular filtration rate, late nephrology access, and insufficient pre-dialysis dietetic care during this period ***(15).***
Earlier opinion on dialysis initiation did consider poor nutritional status as a factor to initiate dialysis. However, this was not based on markers of malnutrition but rather signs and symptoms of malnutrition such as anorexia, nausea, and fatigue. However, many reviews on dialysis initiation observed a lack of data on the benefits of early dialysis initiation in patients with low serum albumin level or in improving nutritional status ***(8).***
Dialysis treatment is expected to improve nutritional status for patients with a more liberal protein prescription compared to the pre-dialysis stage. However, dialysis treatment is cited to contribute to malnutrition burden, and newly dialyzing patients are at risk of the early mortality attributed to malnutrition as evidenced by diagnostic assessment of nutrition risk screening using SGA, low body mass index (BMI), low mid-arm muscle circumference (MAMC), low albumin, low cholesterol levels, and reduced food intake ***(9).***

Iatrogenic Factors of Malnutrition:

ESKD patients with pre-existing malnutrition on maintenance dialysis become additionally vulnerable over time to the catabolic effects of the dialysis treatment, which predispose the patient to greater mortality and morbidity in long-term dialysis. The concern is that the presence of poor nutritional status in dialysis patients predicts increased mortality risk ***(10).***
Iatrogenic malnutrition or “physician-induced malnutrition” is the development of malnutrition arising from medical procedures, pharmacological treatment, prolonged hospitalization, nosocomial infections, or delayed

wound healing. Similarly, aspects of the dialysis procedure contribute to malnutrition, which is unavoidable as it occurs as part of the treatment ***(13).***

Dialysis-Induced Nutrient Losses:

The dialysis process is instrumental to chronic nutrient losses, particularly protein and amino acids. About 6–12 g of amino acids and 7–8 g of protein losses occurring during each dialysis session may contribute to hypoalbuminemia, a strong predictor of malnutrition and mortality. Optimal dietary protein intake (DPI) may replenish low plasma amino acids ***(11).***

However, DPI inadequacy is a common issue in HD patients, affecting 32–81% of HD populations globally. Suboptimal DPI associated with dialysis-induced amino-acid losses promotes protein catabolism through increased whole-body and muscle protein proteolysis ***(16).***

Nutrient losses via dialysis depend on the mechanism of solute removal and the pore size of the dialyzer membrane, which determines solute removal. However, increasing the pore size of dialyzer membranes to enable greater removal of middle molecules also increases involuntary albumin losses, estimated between 2 and 14 g depending on the degree of membrane permeability ***(12).***

As such bio-incompatible membranes, high flux membrane, hemofiltration (HF) and hemodiafiltration (HDF) techniques, or multiple dialyzer reuse practiceinduce greater membrane permeability and facilitate greater losses of amino acids into the dialysate ***(17).***

However, these membranes and/or techniques, in addition to increasing the cost burden, induce greater albumin losses of 3.5 to 9.0 g per HD session, along with involuntary removal of vitamins, larger protein molecules, and lipids. The risk–benefit balance by using dialyzer membranes with greater permeability for improved uremic solute removal versus greater albumin losses remains unknown ***(13).***

Similarly, advanced techniques using either HF or HDF may also pose long-term risk of malnutrition development in HD patients. Given that the permissible threshold for tolerance of albumin losses with highly permeable membrane remains unclear, long-term use of MCO or HCO membranes with HDF techniques may pose malnutrition risk ***(15).***

Multiple Dialyzer Reuse:

In low-to-middle-income countries, the practice of dialyzer reuse is common. However, multiple dialyzer reuse may contribute to negative outcomes such as infection risks, biochemical and immunologic reactions, improper sterilization, increased membrane permeability, and loss of performance leading to inadequate dialysis adequacy. These issues are believed to arise from the reprocessing procedure involving sanitizing agents. However, several studies have indicated that single, minimal (>6 times), or multiple dialyzer reuse carries no impact on dialysis adequacy, body weight, and serum albumin level ***(9).***

Dialysis-Induced Inflammation:

Many factors lead to inflammation in HD patients such as biocompatibility of the dialyzer membrane, infection related to dialysis access, and impure dialysate containing cytokine-inducing substances labelled as endotoxins. Whether dialysis access directly contributes to malnutrition has not been shown. Arteriovenous fistula (AVF) failures are not influenced by markers of poor nutritional status except for high cholesterol and low normalized protein catabolic rate (nPCR) levels ***(17).***

HD patients with catheter access compared to fistula and graft had significantly higher malnutrition–inflammation score (MIS) and lower serum albumin levels. In fact, patients with AVF have 52% greater survival rate compared to those on central venous catheter (CVC) irrespective of nutritional status, although malnutrition was found to lower survival rate by 2% ***(11).***

Instead, catheter rather than graft and fistula access appears to be a significant predictor of greater inflammatory response, and it is associated with the highest all-cause mortality rate mediated by infection. Therefore, the route of dialysis access is rather associated with inflammation and mortality risk, whereby presence of malnutrition may influence the survival rate ***(14).***

Direct effects of the membrane, the extent of complement stimulation induced by the membrane, and the degree of eosinophilia associated with the clearance of cytokines determine the magnitude of the inflammatory response during dialysis. Inflammatory marker levels may be modulated by different types of dialyzer membranes ***(12).***

Generally, the high-flux dialyzer membrane and HDF technique are associated with lower inflammation grade in HD patients when compared to the low-flux dialyzer membrane. These differences are attributed to processing technology for structuring and composition of the membrane, conferring attributes to the dialyzer in terms of biocompatibility, water permeability, clearance, and appropriate sieving coefficients for myoglobin or albumin ***(10).***

Inflammation also occurs with dialysate contamination by microorganisms, which produce endotoxins that pass through the dialyzer membrane and enter into blood circulation, amplifying the production of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α. Infected or old clotted grafts may also contribute to inflammation. Of note, these middle molecules such as IL and TNF-α are not effectively removed by dialysis treatment with low-flux membrane and are accumulated ***(15).***

Overall, dialysis patients are vulnerable to oxidative stress with a marked increase in reactive oxygen species (ROS) production and antioxidant depletion. ROS induces activation of nuclear factor kappa B (NF-κB), which is translocated to the cell nucleus stimulating cytokine production, in turn causing inflammation. Indeed, HD patients have pronounced NF-κB gene expression compared to a healthy population ***(8).***

Another impact of the HD treatment is the activation of polymorphonuclear white blood cells, which trigger production of ROS and other pro-oxidants. Indeed, increased indices of oxidative damage along with decreased indices of antioxidant defence have been observed in HD patients post-dialysis ***(13).***

Low antioxidant levels in HD patients may also occur from limited vegetable and fruit intakes preventing hyperkalemia. Resultant low intakes of vitamin A, C, and E and selenium would affect antioxidant defence mechanisms. Additionally, involuntary removal of vitamins also occurs with every HD session ***(16).***

When malnutrition coexists with inflammation in dialysis patients, the combination of both conditions is known as malnutrition–inflammation complex syndrome. The inflammation results in a reduction in albumin production in the liver and fosters poor appetite, a non-iatrogenic factor implicated in malnutrition ***(17).***

Efficacy of Uremia Correction:

A major aim of dialysis therapy is to remove uremic waste products. However, dialysis only reduces uremic burden through partial removal of uremic solutes. Incomplete clearance of uremic solutes and the generation of urea from both dialysis-induced tissue degradation and dietary proteins contribute to uremic solute accumulation ***(15).***

Excessive uremic solute burden influences amino-acid and protein metabolism by inhibiting transamination activities of enzymes such as threonine dehydratase and alanine and aspartate transferases, impairing membrane transport, inhibiting protein binding, and promoting muscle wasting ***(14).***

The removal of uremic solutes depends on dialyzer membrane permeability. As mentioned earlier, uremic solutes with low molecular weight such as urea and creatinine are efficiently dialyzed via a low-flux dialyzer membrane, whereas membranes with higher permeability allow for greater clearance of small and large middle molecules ***(12).***

However, the threshold for clearance depends on uremic gains on non-dialysis days and total clearance achieved from the previous HD session. Both these factors would determine the severity of uraemia in HD patients. Aside from the permeability of the membrane, total clearance of uremic solutes is also determined by dialysis adequacy, dialysis frequency, and duration of dialysis session ***(15).***

Dialysis Adequacy:

Uremic solute clearance depends on dialysis adequacy, which refers to the frequency and duration of dialysis. Expert guidelines for optimal uremic solute removal favour a three- to five-hourly dialysis session provided

three times weekly in order to meet dialysis adequacy by achieving a Kt/V urea of 1.2, which designates the dialyzer urea clearance (K), time on dialysis (t), and total body water (V) ***(9).***

Of note, the calculation of Kt/V urea is based on urea, a surrogate marker for clearance of small solutes. It does not represent removal of the more detrimental larger uremic solutes. Inefficient removal of uremic toxins via dialysis is suggested to induce taste alteration in HD patients, which contributes to malnutrition ***(13).***

Dialysis Frequency:

Increasing the thrice-weekly frequency of dialysis sessions to >4 times may support better management of fluid removal and lower systolic blood pressure, as well as improve QoL. Alternately, a shorter but increased frequency of dialysis provided by six HD sessions two-hourly per week may benefit toward greater removal of uremic solutes, as shown in patients with lower trends in pre-dialysis serum levels of creatinine, urea, uric acid, and protein-bound solutes such as indole-3-acetic acid and indoxyl sulfate ***(8).***

However, serum albumin levels and post-dialysis weight did not improve for these patients. In contrast, many authors observed improved weight, BMI, and serum albumin status along with decreased serum CRP in patients converting to four HD sessions four-hourly per week from the standard dialysis regime by six weeks. Dietary intake also improved albeit non-significantly. This effect may perhaps be explained by improved appetite occurring with greater removal of uremic compounds through more frequent dialysis ***(10).***

In some countries, weekly frequency of dialysis may depend on the patient's access to financial support. For example, dialysis frequency in low-income countries may be offered as two sessions four-hourly per week compared to the standard dialysis of three sessions four-hourly per week in developing countries. Treatment affordability, poor access to nephrology care and dialysis centers, and inadequately equipped dialysis facilities are reasons for lower dialysis frequency ***(17).***

Dialysis Duration:

Increasing the dialysis duration results in greater removal of small and large uremic solutes compared to the standard HD regime. Patients dialyzing for 8 h using a high-flux dialyzer membrane have shown greater total solute removal, dialyzer extraction ratios, and total cleared volumes for urea, creatinine, phosphorus, and β2-microglobulin compared to patients on standard dialysis, and this occurs without affecting dialysis adequacy ***(11).***

Nutritional marker improvements through higher serum albumin and hemoglobin levels and lower white blood cell count appear to be associated with longer dialysis duration, as indicated from combined data of the three DOPPS. These improvements may be explained by greater removal of both small and large solutes with longer hours of dialysis ***(16).***

Efficacy of Metabolic Acidosis Correction:

Metabolic acidosis develops in the early stages of CKD from the kidney's inability to excrete non-volatile acids and synthesize bicarbonate to maintain acid–base balance. HD treatment aims to correct metabolic acidosis via bicarbonate concentration of the dialysate, ultrafiltration rate, dialyzer membrane surface area and permeability, blood and dialysis flow rate, transmembrane concentration gradient set by the patient's serum bicarbonate level and bicarbonate availability from the dialysate, and dialysis adequacy through maintaining the pre-dialysis serum bicarbonate levels between 24 and 26 mmol/L as recommended by current opinion ***(14).***

However, metabolic acidosis correction depends on patient-related determinants such as intradialytic weight gain, acid generation from high protein intake, or gastrointestinal losses of bicarbonate. Individual fluctuation in patients' bicarbonate levels challenges optimum management ***(13).***

Metabolic acidosis contributes to malnutrition by reducing protein synthesis and increasing muscle degradation. The malnutrition pathway in HD patients involves protein catabolism, secondary insulin resistance, inflammation, and increased serum leptin levels. Lines of evidence using animal and human studies explain that increased muscle breakdown occurs during metabolic acidosis via two mechanisms ***(15).***

These involve increased activation of branched-chain ketoacid dehydrogenase (BCKAD) and the ATP-dependent ubiquitin–proteasome system (UPS) pathway. Importantly, acidosis stimulates increased gene transcription and activity of BCKAD enzyme to degrade the branched-chain amino acids (BCAA), namely, leucine, isoleucine, and valine. BCAAs are important precursors for protein synthesis and are mainly metabolized in the muscle ***(9).***

Increased BCAA oxidation, therefore, is the basis for a higher protein requirement for HD patients. However, metabolic acidosis concomitant with dietary insufficiency and uremia further exacerbates protein catabolism in dialysis patients. Metabolic acidosis activates UPS by increasing gene transcription of the proteasome and ATP-dependent ubiquitin, components involved in the muscle protein degradation pathway. This chain leads to increased caspase-3 activity which promotes cleaving of muscle fibres, resulting in poor muscle mass ***(17).***

Additionally, the acidic environment affects insulin binding to receptors, thus reducing tissue sensitivity to insulin and affecting glucose uptake. Separately, metabolic acidosis also inhibits the anabolic effect of insulin, causing muscle depletion in dialysis patients. Moreover, cell culture studies have shown that TNF-α and interleukins are generated in an acidic environment, triggering an inflammatory response ***(12).***

The impact of metabolic acidosis on nutritional status of HD patients by assessment of serum bicarbonate levels may present anomalies in interpretation. In different malnourished HD populations, serum bicarbonate levels of >23 or >27 mmol/L have been associated with greater mortality risk. As malnutrition is a confounding factor for serum bicarbonate level, there is no ideal serum bicarbonate level that fits all dialysis patients ***(15).***

Non-Iatrogenic Causes of Malnutrition:

Comorbid non-iatrogenic factors may also contribute to malnutrition development in dialysis patients. These non-iatrogenic factors are elaborated on in the sections below.

Suboptimal Dietary Intake:

Suboptimal dietary intake is a primary contributing factor to malnutrition and is associated with increased mortality in HD patients. Adult recommendations for dietary energy intake (DEI) and DPI to achieve nutrient adequacy have been proposed for HD patients by several expert groups, and these generally fall within 25–35 kcal/kg ideal body weight (IBW)/day for DEI and 1.0–1.2 g protein/kg IBW/day for DPI ***(14).***

Requirements factor in criteria to maintain physiological balance, prevent deficiencies from dialysis-induced nutrient losses, and reduce risk of malnutrition and mortality. However, achieving DEI and DPI adequacies remains a challenge for HD patients with intakes falling below recommendations as indicated by many studies. This is evidenced by 70–90% of global HD populations reported with DEI inadequacy, whereas DPI inadequacy ranges between 30% and 80% ***(15).***

Suboptimal DEI is of greater concern than DPI inadequacy, as gluconeogenesis is implied. Three studies reported HD patients achieving DPI adequacy >1.2g/kg/BW but failing to meet DEI adequacy. Insufficient DEI, despite DPI adequacy, predisposes patients to negative nitrogen balance, resulting in both dietary protein and muscle protein to be diverted to fuel body energy requirements ***(10).***

Additionally, amino-acid losses occurring through the dialysis procedure affect protein synthesis, triggering muscle proteolysis to generate amino acids if there is low DPI. Of concern, suboptimal dietary intake bears a negative impact on the survival rate of HD patients as indicated by some studies reporting patients with poor DEI and DPI ***(16).***

Recent metabolomics studies reported higher concentrations of 3-hydroxybutyrate and tartrate along with low creatinine appearing in patients with protein energy wasting. These metabolites are linked to gluconeogenesis and may be conditional to suboptimal DEI and DPI intakes ***(9).***

The background of dietary inadequacy observed in HD patients may be attributed to monotonous dietary patterns, poor diet quality, anorexia, and alterations in taste. A monotonous diet defines a dietary pattern with minimal variety of food groups. Suboptimal DEI from reduced food intake also affects patient adequacy for other essential nutrients, as the overall diet quality falls ***(17).***

Taste Alterations:

Low palatability of diets is underscored by taste alterations experienced by HD patients, and this factor reportedly affects 31–44% of HD populations. Taste alterations experienced by HD patients may be explained by food aversion learning. Aversions toward protein-rich foods such as meat have been significantly associated with enhanced metallic taste in patients also reporting poor appetite ***(8).***

Clearly, taste alterations in HD patients develop food aversion learning, which impacts appetite and reduces overall diet quality, thus contributing to malnutrition. The reduction in taste perception may also be related to zinc deficiency ***(13).***

Poor Appetite:

HD patients reporting poor appetite experience significantly higher frequency of hospital admissions, longer duration of hospitalization, poor QoL, and nutritional outcomes such as lower normalized protein nitrogen appearance levels and high inflammatory marker levels than those reporting good appetite. The immediate impact of poor appetite is reduced dietary adequacy and increased risk of malnutrition ***(11).***

The mechanism for poor appetite may be explained by changes in appetite hormones in HD patients. Ghrelin, an orexigenic hormone mainly secreted by the stomach, regulates appetite by stimulating spontaneous food intake. Ghrelin present in its active form as des-acyl ghrelin has an orexigenic effect, whereas acyl ghrelin as ghrelin in its inactive form is the main orexigenic molecule ***(15).***

Des-acyl ghrelin may have a negative effect on appetite, whilst high acyl ghrelin levels associated with adiposity indicate better nutritional status. Moreover, an association among ghrelin, inflammation, and nutritional status has been reported ***(14).***

Leptin, an adipokine, has an inhibitory effect on appetite in normal metabolism. However, leptin's role in regulating appetite in CKD is controversial. Hypoleptinemia has been associated with malnutrition in HD populations although its mechanistic involvement in causing poor nutritional status is unknown ***(12).***

Applying this hypothesis to the CKD population, it may be inferred that malnourished HD patients with low BMI will have less leptin secreted by adipocytes, whereas the reverse may occur with better nutritional status and higher BMI ***(16).***

Insulin Resistance:

Insulin resistance is implicated in the etiology of malnutrition in HD patients. Insulin at physiological levels bears both catabolic and anabolic effects on skeletal muscle. Insulin's anabolic role is to promote BCAA transport and regulate protein synthesis in the muscle. Another anabolic role of insulin is facilitating glucose transport and uptake by muscle tissues ***(17).***

Reduced insulin secretion by the pancreatic β-cells or impaired tissue sensitivity to insulin at receptor and post-receptor levels in the heart, liver, or muscle are two pathways of insulin insufficiency. More commonly, "uremic insulin resistance" through inflammatory pathways may occur from insufficient removal of dialyzable uremic solutes ***(15).***

Of relevance, insulin resistance at receptor levels is traced to defects in the insulin receptor signalling pathway arising from metabolic derangements accompanying kidney disease such as uremia, metabolic acidosis, anemia, and inflammation.Insulin resistance is associated with peripheral resistance of glucose uptake at the skeletal muscle site and manifests as impaired insulin signalling through the phosphorylation of insulin receptor substrate-1, which inhibits tyrosine kinase activity at the insulin receptor ***(8).***

Reduced insulin sensitivity affects BCAA transport, blunting the anabolic effect of insulin for decreasing skeletal muscle breakdown. Depletion in BCAA due to amino-acid losses via dialysis, along with suboptimal dietary intake led to increased proteolysis to supply amino acids needed for protein synthesis. Therefore, insulin resistance promotes muscle proteolysis, and this association is evident in HD patients with studies reporting a positive correlation between insulin resistance and muscle loss ***(10).***

It is, thus, clear that, in ESKD patients, apart from chronic suboptimal food intake, gluconeogenesis may also be driven by insulin resistance associated with inflammation, uremia, and metabolic acidosis. Gluconeogenesis is a normal adaptive catabolic process to produce energy ***(15).***

Protein sparing under conditions of energy sufficiency occurs as the primary protein function for tissue synthesis and repair. With dietary energy insufficiency, amino acids and proteins derived from dietary protein or breakdown of skeletal muscle during starvation become new substrates for energy. As HD patients are known to have suboptimal food intake, increased gluconeogenesis in these patients stimulates muscle proteolysis, leading to greater risk of malnutrition ***(9).***

Psychosocial Factors:

Psychosocial factors may negatively impact physical and emotional status, QoL, and nutritional status in HD patients ***(11).***

1. **Depression:**

Depression is reported to be prevalent in 6% to 84% of HD patients and arises from loss of the provider role within a family, unemployment, lack of social support, reduced mobility, physical strength, cognitive ability, and sexual function. Additional factors are anxiety and stress from the burden of kidney failure followed by fluid and dietary restrictions, which are significantly associated with poor QoL in these patients ***(15).***

2. **Lack of Social Support:**

ESKD patients exist in a complex matrix of relationships with family, friends, healthcare professionals, and financial support. The quality of emotional and financial support provided by their social network influences stress management, QoL, health-promoting behaviours, malnutrition, and mortality in HD patients ***(13).***

HD patients lacking social support have higher prevalence of diminished appetite, reduced physical functioning, and poor adherence to HD treatment ***(16).***

HD patients with poor social support are more likely to experience serum albumin <3.5 g/dL. In contrast, HD patients with social support can achieve better social interactions and coping mechanisms toward kidney disease, as well as fewer depression symptoms. Ultimately, presence of social support enables patient self-efficacy to reach better health status ***(14).***

3. **Financial Constraints:**

Financial constraints commonly faced by HD patients may be attributed to physical limitations to perform work tasks imposed by treatment and time commitments to dialysis treatment. With unemployment, HD patients are dependent on financial support from caregivers or welfare agencies. Incurring financial dependence triggers loss of self-esteem and depression, leading to poor self-efficacy toward health management. The consequence of limited financial resources is suboptimal dietary intake ***(15).***

The influence of financial status on dietary intake is unclear but forms a factor contributive to malnutrition. Higher SGA and MIS scores of patients indicative of malnutrition are associated with socioeconomic-related nutritional barriers such as difficulty in purchasing food and requiring assistance in meal preparation. Both factors highlight the impact of financial constraints on nutritional status of HD patients ***(8).***

4. **Decreased Physical Functioning:**

Comorbidities associated with CKD such as sarcopenia, vascular dysfunction, inflammation, and malnutrition negatively impacts the three components of physical functioning which are related to body functions and structure, ability to perform, and participation in physical activity ***(9).***

Fatigue is central to the reduced physical capacity to perform activities of daily living by HD patients and contributes to malnutrition. The dialysis process itself may cause fatigue, stiffening of joints, and muscle cramping, thus affecting work task performance. Indeed, fatigue is reported to affect the ability to prepare meals as indicated by majority of HD patients reporting "being too tired to prepare meal" as a barrier toward dietary adherence, and this barrier was associated with lower DEI ***(11).***

Malnourished HD patients, identified using Mini Nutritional Assessment < 19 and SGA > 8, have poor activities of daily living score, suggesting that ability to perform simple daily tasks is affected in these patients ***(12).***

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