Interventions for Hemodialysis Patients

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The hemodialytic clinic must today be directed towards a greater biocompatibility tecnology , the evaluation of the most valid tools to evaluate the nutritional status of patients on every kind of extracorporeal substitutive treatments. Good nutrition is a cultural background that must represent the daily routine of nephrologists. In our opinion, the loss of amino acids up to 1 kg / year is a good starting point. Many parameters used for nutritional outcomes are uncertain and by now the figure of the nutritionist must support tthe nephrologist from pre-dialysis, to dialysis and also in the course of the transplant.

Keywords: aminoacid losses, hemodialysis, new nutritional pa

1. Ideal Diet for Hemodialysis Patients

Advice for HD patients[1][2] has remained unchanged for many years and the diet still prescribed today for thrice weekly HD regimens envisages a protein intake of 1.2 g/kg/day, 30-35 kcal/kg/day, sodium intake < 3–5 g/day, phosphate intake < 1000–1200 mg/day and potassium intake 2000 mg/day. The correct intake of phosphate and potassium is difficult to establish as this is affected by dialysis adequacy, the quantity of phosphate and potassium binding and state of the uremic microbiota. The use of lanthanum carbonate as a phosphate binder leads to a decreasing microbial diversity and lower network complexity[2][3]. In an incremental/infrequent HD strategy[4], whilst the exact protein intake in a twice weekly hemodialysis has not yet been established, there is agreement that protein intake should be 0.6 g/kg/day (50% animal proteins)[5][6]. However, the choice of infrequent HD protects RKF through use of high-flux and biocompatible membranes, particularly hemodiafiltration, use of ultrapure dialysate, a low-protein diet, and careful monitoring of metabolism and blood pressure[7].

2. Replacing Amino Acid Losses by Hemodialysis

An important issue has recently emerged with regard to the loss of amino acids (AAs) in dialysate. Indeed, due to their low molecular weight, AAs are lost in industrial quantities over one year of thrice weekly hemodialysis, particularly when using methods such as hemodiafiltration and hemofiltration, in which additional convective losses occur due to ultrafiltration. Recently, a study group on AAs kinetics in extracorporeal methods showed annual losses > 800 g/year in thrice weekly hemodialysis patients with a consequent, significant loss of lean body and, in particular, muscle mass protein[8][9]. Considering the more contained loss of Total AAs (TAAs) manifested using high-efficiency hemodialysis with a surface dialyzer area of 1.8 m^2 over a 240-minute session, losses could be managed by varying dialytic strategy as shown in Table 1.

Table 1. Forecast Losses of Total Amino Acids (TAAs) through hemodialysis according to different timings and regimens.

Session Time Schedule	TAAs losses/g/year
Thrice weekly, 4 hours	800—810
Four-Fold Weekly, 4 hours	1000—1100
Long Thrice Weekly Hemodialysis, 8 hours	2000—2100
Daily Hemodialysis with time schedule of 2.5–3 hours	1000—1200

The most severe metabolic consequences likely result from loss of essential amino acids (EAAs) such as threonine, tryptophan and lysine and from Non-Essential amino acids (NEAAs) such as tyrosine, aspartic acid, serine, glutamic acid and glycine, resulting in the onset of hypercatabolism and threatening muscle mass loss. Loss-replacement nutritional supplements have been proposed, with keto analogues being used to replace amino acids lost during hemodialysis. Keto analogues are made up of calcium salts, leucine, isoleucine, phenylalanine, valine and Ca-hydroxy-methionine, L-lysine, L-threonine, L-histidine, and L-tyrosine (alfa-kappa, Ketosteril ®, Fresenius Kabi, Bad Homburg, Germany), although taken alone are not sufficient to replace amino acid losses in HD patients. Moreover, supplementation may result in excessive doses of nitrogen, with each tablet containing 337 mg of this element; i.e., calculated on the dose recommended for 70 kg body weight, each patient would consume approx. 470 mg/day nitrogen, also implicating a potential interference with calcium-phosphorus metabolism (such as hypercalcemia) due to a higher calcium intake, with each tablet containing 45 mg calcium; i.e., for 70 kg body weight, an intake of approx. 570 mg/day calcium. This type of product should only be used in advanced stages of chronic kidney disease (CKD4-CKD5) in patients adhering to a very low protein diet regimen (VLPD)[10][11]. In a paper by Bellizzi et al., nephrologists and nutritionists are warned to monitor for probable poor compliance, particularly if the low protein diet is associated with AA intake through keto-analogues. Indeed, in patients prescribed a higher number of tablets or sachets (8–12 per day), compliance with this schedule after six months was limited to 64.5%[12]. Moreover, keto-amino-acid analogues represent a considerably higher cost than other commercial products (over EUR 4000 per year), and treatment could be successfully replaced by a tailored, more efficient and less expensive amino acid supplement EUR 600–700 per year). Very few trials have been conducted to date to evaluate AA supplementation in hemodialysis patients; based on our previous experience[13], the daily administration of 5 grams of a combination of 6 EAA, 2 NEEA, 2 BCCAA, with no metabolic accelerators, plus vitamins B1 and B6 for three months, obtained highly promising results (Table 2).

Table 2. Preliminary trial of a group taking AA supplementation compared to a placebo control group[13].

	Control Placebo Group = n.14		**Study Supplemented Group = n.15**	
	Baseline	**3 Months**	**Baseline**	**3 Months**
Body Weight, Kg	59.1 ± 12.7	58.8 ± 5.8	69.8+13.7	68.9+13.5 [a]
BMI, kg/m^2	25.9 ± 5.8	25.4 ± 5.8	28.6 ± 5.6	28.5 ± 5.5
eKt/V	1.39 ± 0.22	1.38 ± 0.16	1.23 ± 0.26	1.34 ± 0.16
ePCR, g/kg/d	0.9 ± 0.2	0.9 ± 0.2 **	0.9 ± 0.2 [b]	1.1 ± 0.2 ** [b]
Phase angle, (°)	4.8 ± 1	4.8 ± 0.7	4.6 ± 0.9	4.9 ± 1
FFM, kg	41.5 ± 6.6	42.1 ± 6.0 *	39.5 ± 6.6 *	38.1 ± 6.3 *
FM, kg	27.9 ± 10.6 *	27.7 ± 11.6 *	22.1 ± 7.8 *	22.6 ± 7.5*
Albumin, g/dL	3.19 ± 0.16	3.09 ± 0.31 ***	3.08 ± 0.29 [c]	3.58 ± 0.23 *** [c]
Total Proteins, g/dL	5.91 ± 0.49	5.95 ± 0.46 *	5.70 ± 0.41 [c]	6.43 ± 0.73 *[c]
Hb, g/dL	11.0 ± 0.7	10.6 ± 0.6 ***	10.7 ± 0.9 [a]	11.7 ± 0.8 ***[a]
ERI, U/Kg/week/g. Hb	15.2 ± 14.8	14.7 ± 16.8 [a]	13.1 ± 12.8	12.7 ± 15.5 [a]
BUN, mg/dL	60.1 ± 13.7	59.5 ± 14.9	60.9 ± 0.8	64.4 ± 0.7

CRP, mg/L	13.6 ± 17.1	11.2 ± 12.2 **	8.7 ± 7.3 [b]	3.8 ± 3.1 **[b]
Tot. Ig, mg/dL	1359 ± 237	1304 ± 222	1249 ± 548	1549 ± 470 [b]
C3, mg/dL	98.6 ± 27.6	93.8 ± 10	41.5 ± 6.6	97.3 ± 12.8

BMI (body mass index); eKt/V (equilibrated Kt/V); ePCR (equilibrated protein catabolic rate); FFM (free fat mass); FM (fat mass); ERI (erythropoietin resistance index); BUN (blood urea nitrogen); CRP (C reactive protein); Ig (immunoglobulin). a: $p < 0.05$, b: $p < 0.01$, c: $p < 0.001$ vs baseline; *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$ vs Control Group.

The results of this study led us to recommend the administration of a new amino acid combination of 20 main amino acids (EAAs, NEAAs and BCAAs), vitamins and micronutrients tailored to the quantities and qualities of amino acids lost through dialysis at the end of a hemodialysis day (Amino-HD, Professional Dietetics, Milano, Italy)[14], with administration during the interdialytic interval of an amino acid solution containing 10 EAAs with mitochondrial metabolic accelerators such as malic and succinic acids, group B vitamins and a minimum calorie intake (Amino-Ther, Professional Dietetics, Milano, Italy). Neither combination contains nitrogen or calcium. These new amino acid mixtures may increase cellular oxygen uptake (an effect produced by nitric oxide NO mediated by PGC-1alpha), the main regulator of mitochondrial biogenesis, thus promoting biogenesis and mitochondrial function by activating catabolic processes of amino acids. These new combinations contain a carefully calibrated dose of the aromatic amino acids tyrosine, phenylalanine and tryptophan, which are converted into protein-bound uremic toxins (PBUTS). These observations were made by comparing the difference between AA levels in plasma from arterial blood of HD patients and healthy subjects[8]. This metabolic effect could slow down or prevent decline into malnutrition and/or protein-energy wasting in patients required to sustain years of treatment and avoid the use of amino acids in muscle mass to produce energy[15]. A post-hoc analysis[9] confirmed a severe loss of AAs during hemodialysis and/or hemodiafiltration (HDF), with detection of a marked loss of total AAs (5 g/session), corresponding to more than 65% of all AAs. Regarding individual AAs, glutamine displayed a consistent increase (+150%), whereas all other AAs decreased after 12 months of HD/HDF. Only a few AAs, such as proline, cysteine, and histidine maintained normal levels. The most severe metabolic consequences may result from losses of EAAs such as valine, leucine and histidine, and from NEAAs including proline, cysteine and glutamic acid, eliciting the onset of hypercatabolism threatening muscle mass loss. In our patients, dialysis losses, together with the effect of chronic uremia, resulted in a reduction of fundamental EAAs and NEAAs, which over 12 months progressively led to a deterioration of lean mass, leading towards sarcopenia. Therefore, the reintroduction of a correctly balanced and tailored AA supplementation in patients undergoing HD to prevent or halt the decline of hypercatabolism into cachexia, is recommended.

3. Reduction of Hypercatabolism by Hemodialysis

Although in the majority of cases, dialysis sessions are well tolerated, in HD, onset of the compartmental imbalance is asymptomatic, rapid and violent. Intra-dialysis inflammation plays a fundamental role due to contact with dialysis membranes, even the least biocompatible, by means of which activation of a class of monocytes responsible for the release of cytokines is inevitable. Hypercatabolism in dialysis patients is related to intradialytic loss of amino acids as well as cytokine activation[16][17]; interleukin-6 plays a central role in regulating whole-body, muscle and hepatic protein turnover during hemodialysis. CD14 + CD16 + lymphocytes play a central role in the release of cytokines (IL-1 IL-6, TNF-α)[18]. Furthermore, at the end of the session, a post-dialysis rebound of numerous molecules occurs, the most widely studied of which is urea, largely due to the ease of detection. This rebound of uremic toxins is well known and is first manifested by the redistribution of molecules such as urea, phosphates and β2-microglobulins from several cellular and intracellular compartments and in plasma water. The magnitude of this compartment redistribution is directly related to the purifying dialytic intensity, resulting in consequent hypercatabolism and further energy expenditure. It is well known that a short standard hemodialysis treatment corresponds to a protein catabolic rate (PCR) > 1.4 g/kg/day, with this value corresponding to the daily protein intake required by the patient to compensate for the increase in PCR linked to dialysis hypercatabolism[19][20].

To conclude this chapter, it should be highlighted how the oxidative stress manifested in chronic kidney disease is exacerbated by HD treatments using any type of dialysis membrane, through triggering of platelet activation (release of reactive oxygen species, ROS), failure to use ultrapure dialysate (endotoxins cross the membrane from poor quality dialysis water), or use of an acetate buffer rather than bicarbonate (ROS release)[21]. It still remains a very difficult task to prevent hypercatabolism produced by hemodialysis, although satisfactory results may be obtained by using less

biocompatible membranes or membranes that reduce the passage of contaminants from dialysis liquid. Lympho-monocyte activation occurs in the presence of all types of HD membranes, thus underlining the need to use optimum sterilization methods, ultra-pure or sterile dialysis liquid flow and the most biocompatible biochemical composition to the hemodialysis machine[22][23][24][25][26][27][28][29][30][31][32][33].

4. Replacement of Vitamin Losses

Dialysis patients frequently present with reduced levels of a broad range of vitamins[34]. Reports focused on vitamin losses present in the literature relate solely to a few studies from the 1980s, mainly because the majority of studies have concentrated on the loss of vitamin D in its various forms. The results of these studies are of scarce utility in providing a tailored personalized therapy with vitamin D (oral or intravenous/). The dosage of other vitamins (vitamins C, A and E) for the treatment of renal osteodystrophy is highly complex, lengthy and expensive, involving the use of reverse-phase high performance liquid chromatography. No significant reductions have been observed during any extracorporeal therapeutic option in vitamin A, B1, and B12[35]. The only loss reported was for vitamin C, particularly when using hemodiafiltration methods of 8–230 µg/session, resulting in a significant reduction of plasma levels from 1.87/µ/mL to 0.98 µg/mL[36]. Vitamins C and E are both characterized by anti-oxidative properties, with vitamin C acting as an enzyme cofactor and enhancing mobilization of the ferrous form of iron to transferrin, thus increasing bioavailability and avoiding limitation of administration to prevent secondary oxalosis[24][37]. As a general rule, HD patients do not manifest losses of vitamin B1, B12, C and folate, as these are replaced intravenous at the end of a HD session, or orally with cycles of approx. 15 administrations three times per year[38].

5. Other Intravenous Supplements

When faced with an evident state of malnutrition or PEW, intravenous nutritional and caloric support should be provided. Ideally, this should be administered throughout the entire duration of the extracorporeal session[39][40][41]. Parenteral nutrition administration must provide an adequate calorie intake (approx. 1000 kcal) from lipids and albumin, and the administration of amino acids during the session preferably avoided as these remain in the circulation for several minutes[42] and are eliminated by diffusion and ultrafiltration diffusion through the dialysis membrane[43]. This often produces nausea during the dialysis session. Furthermore, it remains unclear whether significant advantages regarding baseline characteristics or nutritional status are registered following administrating of intravenous nutrition during HD treatment[44]. It may therefore be advisable to administer nutrition after the hemodialysis session. Intra-parenteral administration should continue over a period of four to six months in order to restore a positive metabolic balance even in severely malnourished patients[45]. However, the majority of infusions currently marketed contain amino acids. These solutions are lipid solutions in the form of binary, ternary mixtures with the presence of medium- or long-chain triglycerides at 10%, 20%, 30% (10 kcal/g) essential fatty acids, vegetable oils such as refined soybean and olive oil, fish oil containing Omega-3 and vitamin E to avoid rancidity of the lipid solution. Mandatory procedures for intra-parenteral, intra-session administration provide for post-dilution infusion by hemodiafiltration, as this method allows lipid nutrients to be directly administered intravenously without passing through the dialysis filter. The infusion rate of the lipid solution (1800 mOsml/kg) can be readily calculated by 1:6 dilution with the dialysis infusion liquid, thus preventing throughout the hemodialysis session plasma hyper-osmolarity on the venous system, particularly at the arteriovenous fistula[46]. The high costs could potentially be recovered through a reduction in the morbidity and hospitalization of patients in whom undernourishment or PEW have been successfully prevented.

6. Preserving Gut Microbiota in a Uremic Milieu

For many years, the microbiota has been underestimated; however, it is now an acknowledged fact that in advanced uremic stages the microbiota is significantly affected. Chronic kidney disease is characterized by an accumulation of protein-bound uremic toxins (PBUTs) such as p-cresyl sulfate (pCS), p-cresyl glucuronide (pCG), indoxyl sulfate (IxS), and indole-3-acetic acid (IAA). Each of these uremic retention solutes exerts toxic effects, and several have been associated with worsening outcomes in CKD patients, in particular with cardiovascular morbidity and mortality. All four PBUTs originate from the intestinal microbial metabolism, mainly from the aromatic amino acids (AAAs) tyrosine, phenylalanine and tryptophan[47][48][49][50]. These outcomes stem from a state of dysbiosis in bacteriological equilibrium with pathobionts overcoming symbiotic germs and becoming deranged in the tight gastrointestinal junction barrier resulting in an increasingly toxic milieu such as PBUTs, [51]which is highly toxic on a cardiovascular level. This in turn may elicit cardiac damage and nephrotoxicity, endothelial damage and diffuse endothelial injury[52]. Effective, targeted therapies for HD patients have not yet been well defined, with the majority of research work aimed at decreasing the levels of PBUTs rather than specifically curing the uremic microbiota[53]. Some authors have recently suggested the addition of nuts and/or

vegetables to the diet[54][55], whilst others have performed studies on the efficacy of a new intestinal charcoal adsorbent[56]. A recent review by Bao et al. describes the ability of different polyphenols, such as anthocyanin, catechin, chlorogenic acid, and resveratrol, to regulate intestinal microorganisms, inhibit pathogenic bacteria, and reduce inflammation[57]. Another study group conducted a randomized, placebo-controlled pilot study in HD patients to establish whether administration of a symbiotic, either individually or in association with divinylbenzene-polyvinylpyrrolidone (DVB-PVP) cartridge, could reduce the production of uremic toxins[58]. In view of the complexity in establishing full composition of the microbiota, therapeutic trials aimed at correcting uremic dysbiosis are few, unsatisfactory and inconclusive. Despite a series of attempts to date, no effective therapy using prebiotics, probiotics and symbiotics to maintain a healthy microbiota in hemodialysis has yet been defined[59][60]. However, tailored amino acid supplementation may produce a certain rebalancing of the microbiota in the course of chronic diseases including CKD[61].

7. Education and Updating of Health Professionals, Patients and Family Members

The actions of education and updating should largely be directed at the patients' main caregivers, i.e., family members or care assistants who make informed purchases of foods paying particular attention to phosphorus, potassium, and protein content, which are fundamental for dialysis patients. It goes without saying that the use of fresh food is preferable to use of processed foods[62]. Prior to the advent of hemodialysis program treatments, the International Society of Renal Nutrition and Metabolism working group carried out a prospective, interventional study known as the Nutritional Education Program on a total of 160 patients with CKD[63]. It was demonstrated that the actions of those who shop or cook is of fundamental importance in avoiding the purchase of processed foods containing phosphates, potassium, sodium, sulfites, etc., which have preservative, thickening and stabilizing functions[64]. Appropriate nutrition should also provide for an adequate energy intake, in healthy individuals amounting to 31.8 ± 7.0 kcal/kg/day; however, in hemodialysis patients, dietary intake is frequently insufficient, reaching 29.5 ± 6.6 kcal/kg/day[65]. Physical activity in CKD patients should also be included as part of a therapeutic program and be increased[66]. Exercises such as push-ups, pull-ups, crunches, air squats, Pilates, and aerobic endurance exercises designed to increase cardiovascular and respiratory fitness, such as walking or running, are recommended[67].

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