Chapter 18
Nutritional Aspects of On-Line Hemodiafiltration

Pieter M. ter Wee and Denis Fouque

Abstract As renal function deteriorates, worsening of appetite and a decline in the nutritional state is frequently observed in patients with chronic kidney disease (CKD). The term Protein Energy Wasting (PEW) describes a state of decreased body protein and energy stores. PEW is defined as the presence of three out of the following four categories: decreased serum albumin or cholesterol levels, low or a fall in body mass, decreased muscle mass or unintentional loss of dietary protein (and calorie) intake. Besides inflammation, oxidative stress and an altered metabolic and hormonal balance, retention of middle molecular weight (MMW) and protein bound uremic toxins may contribute to the decreased appetite and poor nutritional state in patients with CKD, especially when treated by hemodialysis (HD). In these patients, blood levels of phosphate, which is considered a uremic toxin, are considerably elevated. Of interest, its control in online post dilution HDF is markedly better than in low-flux HD, but comparable to high-flux HD. In HD, loss of amino-acids occurs concomitantly with proteolysis of body stores. As a result, blood levels of amino-acids remain unaltered at the cost of muscle catabolism. As of yet, major differences are not observed between patients who are treated with HD or HDF. Future studies are needed to resolve the question whether treatment with high volume HDF will alleviate PEW in our patients.

Keywords Nutrition • Protein energy wasting • Oxidative stress • Phosphate • Muscle catabolism • Amino acids • Albumin • Appetite

P.M. ter Wee, MD, PhD
Department of Nephrology, VU University Medical Center and ICaR-VU, Amsterdam, The Netherlands

D. Fouque, MD, PhD (✉)
Department of Nephrology Nutrition Dialysis, Centre Hospitalier Lyon Sud, Chemin du Grand Revoyet, Pierre Bénite 69495, France
e-mail: denis.fouque@chu-lyon.fr

M.J. Nubé et al. (eds.), *Hemodiafiltration: Theory, Technology and Clinical Practice*, DOI 10.1007/978-3-319-23332-1_18

Introduction

Chronic kidney disease (CKD) is associated with metabolic derangements and late complications, including a substantially increased risk of all-cause and cardiovascular morbidity and mortality, especially in dialysis patients. Since the increased risk on an adverse clinical outcome is still significant after correction for traditional risk factors such as age, smoking, hypertension, diabetes and lipid abnormalities, other factors may contribute as well. One of these factors is protein energy wasting (PEW), which has been defined as abnormalities in at least three out of four categories: decreased serum albumin or cholesterol levels, low or a fall in body mass, decreased muscle mass or unintentional loss of dietary protein (and calorie) intake [1].

Thus, insufficient intake of nutrients is one of the factors contributing to PEW. Patients with CKD frequently have loss of appetite, which increases in severity during the course of the disease and is worst in dialysis patients [2]. After the start of renal replacement therapy, appetite usually improves, but with ongoing time it drops again progressively. Similarly, as demonstrated by Ikizler et al. [3], spontaneous protein intake decreases in patients with advancing GFR loss, which clearly contributes to the risk of developing PEW and frailty. Although the exact reasons for the loss of appetite and decreased protein intake are at present unknown, it is generally assumed that accumulation of toxic uremic substances is at least partially responsible for these observations. As uremic retention products, especially those in the middle molecular weight (MMW) range, are better removed by (on-line) hemodiafiltration (HDF) as compared to standard HD [4], treatment with HDF may improve the nutritional state in patients with end-stage-renal disease (ESRD).

Hemodiafiltration and Phosphate Removal

Serum phosphate, which is actually a low molecular weight substance, behaves like a MMW compound as it is surrounded by water molecules that makes it water soluble. Indeed, it could be demonstrated that HDF results in a higher clearance of phosphate than standard HD, possibly due to mobilization from a deep compartment induced by the high intradialytical removal of this solute [5]. Comparable results were obtained in a large recent randomized prospective trial (RCT) comparing post-dilution on-line HDF with low-flux HD three times a week HD [6]. In this study, the drop in phosphate could not be explained by changes in the prescribed medication, as the amount of non-calcium containing phosphate binders remained unchanged or tended to decline in HDF patients and increased in individuals treated with HD. Assuming that dietary intake had not changed over time in either group, this observation could indeed be explained by better phosphate removal during on-line HDF. This was confirmed in a recent meta-analysis [7]. Thus, increased phosphate removal could not only contribute to a better phosphate control, but potentially

also to an increased dietary protein intake, a better clinical outcome and a reduced amount of unpalatable phosphate binders. In this respect, it should be mentioned however, that two other large recent RCTS comparing HDF with high-flux HD did not show marked differences in phosphate levels between treatment arms, despite the achievement of high convection volumes in the latter [8, 9].

Hemodiafiltration and Protein Losses

It has been long known that standard HD per se results in a substantial loss of amino acids [10]. Subsequently, Deleaval et al. [11] demonstrated that serum levels of amino acids especially dropped during the first hour of HD and remained constant during the following 3 h. Since it was previously shown that treatment with HD induces proteolysis of body proteins [12], the same authors concluded that the fall in amino acid levels during the part of HD is counterbalanced by substitution from proteolysed proteins, resulting in a stabilizing of blood amino acid levels during the last part of the session [11]. Thus, HD per se might contribute to PEW in at least two ways, first through the loss of amino acids from the blood into the dialysate and second through muscle and whole body protein catabolism during treatment. Similar conclusions may hold true for HDF, as with this technique losses of essential and non-essential amino acids have been reported as well, although a direct comparison between intermittent HDF and standard HD techniques is lacking [13]. Since, however, a lower inflammatory response has been described during HDF than during HD [14, 15], which could result in less catabolism, the long-term outcome of HDF treatment on nutritional status is unclear upfront.

Hemodiafiltration and Nutritional State

In 2005 Bossola et al. [16] reported on a single center experience in which they prospectively followed eight patients for 8 months after switching them from thrice weekly intermittent HD to HDF with on-line regeneration of ultrafiltrate. After 12 months no changes in nutritional parameters were seen, although the malnutrition inflammation score (MIS) tended to improve. In 2006 the results of a 4-years prospective observational study on 31 subjects treated with on-line HDF were reported [17]. Significant changes in normalized protein catabolic rate, albumin, prealbumin, transferrin and creatinine, however, were not observed. By contrast, body mass index, fatty mass and free fatty mass improved in 12 patients after 6 months of treatment with predilution on-line HDF [18]. Likewise, it was demonstrated in a prospective single center study that 3 years of treatment with on-line HDF resulted in an improved appetite and overall well-being, which was associated with increases in dry weight, body mass index and normalized protein nitrogen appearance [19]. In a large cohort study, Vilar et al. [20] showed that

after a 5 year observation period 232 patients treated with on-line HDF had a 0.66 hazard for death compared to 626 patients treated with high-flux HD. Despite these promising findings, however, difference in nutritional status between the groups could not be found. In 15 children who had been treated with growth hormone but still were growth retarded, switching from standard thrice weekly HD to daily predilution on-line HDF for an average period of 20.5 months resulted in catch up growth and a rise in body mass, which was attributed by the investigators to less malnutrition and less cachexia [21]. In a cross over study in 24 patients treated with conventional bicarbonate HD, Matsuyama et al. [22] found that on-line HDF with acetate-free bicarbonate dialysis fluid improved leptin and neuropeptide Y levels together with lower levels of interleukin 6 and C-reactive protein, and a trend towards a higher protein catabolic rate (PCR), which is considered a reliable measure of protein take. From these observations the authors suggested that on-line HDF with acetate-free bicarbonate resulted in a decrease in microinflammation and an improved nutritional status. In 22 patients who were switched from thrice weekly daytime on-line HDF to nocturnal every-other-day on-line HDF for 1 year, a rise in dry body weight was observed, although other markers of nutritional status like normalized PCR (nPCR), albumin and prealbumin did not change [23]. In contrast to the above mentioned results, Orasan et al. [24] recently showed in 44 patients that after switching from standard HD to on-line HDF, both serum albumin levels and nPCR were significantly lower during the HDF period, while body mass index tended to decrease. In a large multi-center RCT (the CONvective TRAnsport Study; CONTRAST), in which 714 dialysis patients were randomized to either low-flux HD or on-line post dilution HDF, both serum albumin and body mass index decreased significantly over time [15], without differences between patient groups. At present results on all-cause mortality of two other large prospective RCTs comparing HD and HDF have been reported, but so far data on nutritional aspects of those studies is limited. Time averaged serum albumin was slightly lower in the HDF group of the Turkish study (3.93 ± 0.24 vs 3.99 ± 0.27 g/dL, $p < 0.001$) [8]. In the ESHOL study there was a slight but significant trend for albumin and dry body weight to decrease in the HDF group as well [9].

Summary and Conclusions

In summary, from the currently available literature it can be concluded that there are no convincing data demonstrating that on-line HDF leads to improvements in the nutritional status of ESRD patients. Although some benefits have been described in observational studies, differences between groups were not found in a large RCT comparing on-line HDF with conventional HD [15]. While most studies showed either no change or some beneficial effects, so far in only one study a negative influence of on-line HDF on nutritional outcome was reported. The disadvantage of an increased loss of nutrients and vitamins, as may occur in high volume HDF, should

be weighed against benefits on inflammatory status, appetite and (less) protein catabolism. Altogether it can be concluded that more research is warranted to finally conclude what the impact of on-line HDF specifically has on the nutritional state of ESRD patients.

Teaching Points

- As renal failure deteriorates, worsening of appetite and nutritional state is frequently observed
- Protein energy wasting (PEW) is defined as the presence of three out of the following four categories: decreased serum albumin or cholesterol levels, low or a fall in body mass, decreased muscle mass or unintentional loss of dietary protein (and calorie) intake.
- Besides inflammation and other contributory factors, accumulation of MMW uremic toxins may contribute to the poor appetite and nutritional state in patients with CKD
- Phosphate control in online post dilution HDF is markedly better than in low flux HD, but comparable to high-flux HD.
- Loss of amino-acids during HDF does not seem much different than during high flux HD
- In ESRD patients, the nutritional state worsens over time, irrespective of the dialysis modality applied

References

1. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–8.
2. Carrero JJ. Identification of patients with eating disorders: clinical and biochemical signs of appetite loss in dialysis patients. J Ren Nutr. 2009;19:10–5.
3. Ikizler TA, Greene JH, Wingard RL, Parker RA, Hakim RM. Spontaneous dietary protein intake during progression of chronic renal failure. J Am Soc Nephrol. 1995;6:1386–91.
4. Wizemann V, Kulz M, Techert F, Nederlof B. Efficacy of haemodiafiltration. Nephrol Dial Transplant. 2001;16 Suppl 4:27–30.
5. Minutolo R, Bellizzi V, Cioffi M, Iodice C, Giannattasio P, Andreucci M, et al. Postdialytic rebound of serum phosphorus: pathogenetic and clinical insights. J Am Soc Nephrol. 2002;13:1046–54.
6. Penne EL, van der Weerd NC, van den Dorpel MA, Grooteman MP, Levesque R, Nube MJ, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST). Am J Kidney Dis. 2010;55:77–87.
7. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. Nephrol Dial Transplant. 2013;28:2859–74.
8. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. Nephrol Dial Transplant. 2013;28:192–202.

9. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macia J, Carreras J, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
10. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM. Amino acid and albumin losses during hemodialysis. Kidney Int. 1994;46:830–7.
11. Deleaval P, Teta D, Vianey-Saban C, Claustrat B, Kopple JD, Fouque D. Early drop and plateau plasma amino-acid pattern during hemodialysis (HD) session. J Am Soc Nephrol. 2007;18:482A.
12. Ikizler TA, Pupim LB, Brouillette JR, Levenhagen DK, Farmer K, Hakim RM, et al. Hemodialysis stimulates muscle and whole body protein loss and alters substrate oxidation. Am J Physiol Endocrinol Metab. 2002;282:E107–16.
13. Ragazzoni E, Carpani P, Agliata S, CCiranna G, Cusinato S, et al. HFR vs HDF-on line: plasmatic amino acid loss evaluation. G Ital Nephrol. 2004;21 Suppl 30:S85–90.
14. Susantitaphong P, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. Nephrol Dial Transplant. 2013;28:438–46.
15. Den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Penne EL, Mazairac AH, et al. Clinical predictors of decline in nutritional parameters over time in ESRD. Clin J Am Soc Nephrol. 2014;9:318–25.
16. Bossola M, Muscaritoli M, Tazza L, Giungi S, Panocchia N, Rossi FF, et al. Switch from bicarbonate hemodialysis to hemodiafiltration with online regeneration of the ultrafiltrate (HFR): effects on nutritional status, microinflammation, and beta-microglobulin. Artif Organs. 2005;29:259–63.
17. Munoz R, Gallardo I, Valladares E, Saracho R, Martinez I, Ocharan J, et al. Online hemodiafiltration: 4 years of clinical experience. Hemodial Int. 2006;10 Suppl 1:S28–32.
18. Savica V, Ciolino F, Monardo P, Mallamace A, Savica R, Santoro D, et al. Nutritional status in hemodialysis patients: options for on-line convective treatment. J Ren Nutr. 2006;16:237–40.
19. Tiranathanagul K, Praditpornsilpa K, Katavetin P, Srisawat N, Townamchai N, Susantitaphong P, et al. On-line hemodiafiltration in Southeast Asia: a three-year prospective study of a single center. Ther Apher Dial. 2009;13:56–62.
20. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol. 2009;4:1944–53.
21. Fischbach M, Terzic J, Menouer S, Dheu C, Seuge L, Zalosczic A. Daily on line haemodiafiltration promotes catch-up growth in children on chronic dialysis. Nephrol Dial Transplant. 2010;25:867–73.
22. Matsuyama K, Tomo T, Kadota J. Acetate-free blood purification can impact improved nutritional status in hemodialysis patients. J Artif Organs. 2011;14:112–9.
23. Maduell F, Arias M, Duran CE, Vera M, Fontsere N, Azqueta M, et al. Nocturnal, every-other-day, online haemodiafiltration: an effective therapeutic alternative. Nephrol Dial Transplant. 2012;27:1619–31.
24. Orasan RA, Patiu IM, Anghel D, Bejan C, Iosub L, Totolici C, et al. Variation of clinical and laboratory features in chronic dialysis patients treated with high-flux hemodialysis after switching to online hemodiafiltration. Int Urol Nephrol. 2013;45:1415–22.