Chapter 5.1

General discussion

INTRODUCTION

Patients with end-stage kidney disease (ESKD) face a wide variety of problems due to the abnormalities that are associated with the uremic syndrome and the dialysis treatment. Despite continuous research and treatment optimization, the clinical outcome of such patients remains poor when compared to the non-renal population.[1-3] The present thesis focuses on three aspects in this patient group: (1) how to assess protein-energy wasting (PEW), in the absence of a gold standard (**chapters 2.1** and **2.2**), (2) investigate the association between several cardiovascular risk factors and clinical outcome parameters in order to identify potential clinical intervention options (**chapters 3.1, 3.2** and **3.3**) and (3) optimization of the treatment of post-dilution online hemodiafiltration (HDF) by investigating the role and feasibility of high convection volumes (**chapters 4.1**, **4.2, 4.3** and **4.4**). For all chapters, the relevance, current understanding, findings and relation with the available literature are described. Furthermore, recommendations and proposals for future research in each area are formulated.

PROTEIN-ENERGY WASTING

Definition and relevance

Protein-energy wasting (PEW) describes a state of decreased body protein mass and impaired energy reserves. It was proposed as the uniform term for this syndrome by an expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) in 2008 to resolve the confusion that was the result of non-uniform and ill-defined terminology in those days in this area.[4] In patients with ESKD, PEW is present in 30-75% as measured by various nutritional indices.[5-7] Importantly, PEW is not synonymous with malnutrition, which refers only to abnormalities due to an inadequate diet.[4] An inadequate intake may result from anorexia, underlying illness, taste abnormalities, loss of dentures, gastropathy, enteropathy, medication and psychosocial problems,[8-12] and plays an important etiologic role in PEW. Other factors, however, such as persistent (micro)inflammation, oxidative stress, acidosis, endocrine disorders and an increased resting energy expenditure are also important contributors in the development of PEW. In subjects treated with hemodialysis (HD), the dialysis procedure itself can contribute to PEW as well.[13-15] PEW is presumed to contribute to an increased mortality and morbidity as well as an impaired quality of life (QOL).[4] Patients suffering from PEW may benefit from supplementation of proteins, energy, trace elements or vitamins, as has been stated by various nutritional guidelines for patients suffering from chronic renal

failure.[16-19] Given its high potential for intervention, it is important that PEW is detected accurately, especially in patients with ESKD.

Lack of a gold standard

The number of nutritional indices appears almost infinite, given the availability of clinical subjective scores,[20,21] biochemical parameters,[22-24] technical measurements,[25-28] dietary recall assessments,[10-12] appetite scores,[12,29] anthropometric measurements[11,24,30] and combinations of the abovementioned tests,[31-33] which are all considered to be nutrition-related. Yet, despite all these scores, the concept PEW lacks a gold standard.[14,34-36] This is underscored by the recommendation in various guidelines to measure PEW by a panel of nutrition-related markers.[16-19] According to the consensus paper of the ISRNM, PEW is present when three out of the following four indicators are abnormal: (1) biochemistry (low serum albumin or transthyretin), (2) body mass (low body mass index [BMI], unintentional weight loss or low total body fat percentage), (3) muscle mass (muscle wasting, reduced mid-arm muscle circumference area or creatinine appearance) and (4) dietary intake (low protein or energy intake).[4] It should be mentioned, however, that this recommendation is expert opinion based (level 5 evidence)[37] and thus, the lack of a gold standard remains. Therefore, in **chapter 2.1** and **chapter 2.2,** we aimed to add evidence in the quest to find the preferred test to assess PEW.

Findings

Eight nutritional indices were compared in the abovementioned chapters: one subjective clinical score (the 7-point scaled Subjective Global Assessment [SGA-7])[38], two objective scores (the normalized Protein Nitrogen Appearance [nPNA][39] and the Geriatric Nutritional Risk Index [GNRI]),[32,40] two biochemical parameters (serum creatinine [sCr], serum albumin [sAlb]),[29] one anthropometric measurement (BMI)[24] and two composite scores (the composite score on Protein-Energy Nutritional Status [cPENS][31] and the Malnutrition Inflammation Score [MIS]).[33] These tests were compared using four different clinical end points, which are all considered important consequences of PEW[4]: all-cause mortality, the occurrence of a cardiovascular event, the occurrence of an infection (all in **chapter 2.1**) and an impaired QoL (**chapter 2.2**). Whereas sAlb and MIS predicted all-cause mortality and infection equally well, the MIS predicted the occurrence of cardiovascular events best. Possibly, this can be partly attributed to the inclusion of a cardiovascular medical history and dialysis vintage in the MIS. Furthermore, MIS had the best relation with QOL. With respect to the latter, it is important to realize that 'functional capacity', which is an important subject in the QOL scoring list,[41] is included in the MIS.

Recapitulation of evidence

From these results, a number of major conclusions can be drawn. First, overall, the MIS associated best with the investigated end points (table 1). From this finding, it can be concluded that a panel of nutrition-related markers indeed appears to be the best method to assess PEW, as is suggested by multiple nutritional guidelines.[16-19] After all, the MIS is a composite score, consisting of 10 items: five subjective elements (dietary intake, gastrointestinal symptoms, functional capacity, decreased fat stores and signs of muscle wasting), two objective elements (change in postdialysis weight and comorbidity plus dialysis vintage), an anthropometric measurement (BMI) and two biochemical variables (sAlb and total iron binding capacity).[33] Furthermore, it is important to realize that the cPENS score is based on the four diagnostic criteria proposed by the ISRNM (sAlb, sCr, nPNA and BMI).[4,31] Given the fact that this score was inferior to MIS, cPENS seems less accurate. This statement is underscored by the inferiority of another score that was based on the 4 diagnostic criteria from the ISNRM[42] when compared to the MIS.[43] Third, the MIS measures more than just inflammation[22] given the absence of a relation between sAlb and QOL, whereas MIS (in which sAlb is 1 out of 10 items) has an adequate relation with QOL.

Table 1. Findings of chapters 2.1 and 2.2.

	All-cause mortality		Cardiovascular events		Infection		QoL
	HCS	*p HL*	*HCS*	*p HL*	*HCS*	*p HL*	*CC*
MIS	0.68	0.65	0.59	0.17	0.63	0.50	-0.28
SGA	0.61	0.42	0.54	0.61	0.57	0.04	0.15
cPENS	0.63	0.002	0.55	0.01	0.59	0.71	0.01
GNRI	0.64	0.73	0.53	0.93	0.60	0.92	0.04
sAlb	0.64	0.95	0.53	0.66	0.60	0.18	0.02
sCr	0.65	0.007	0.59	0.16	0.58	0.22	-0.02
BMI	0.50	0.07	0.51	0.06	0.51	0.70	-0.01
nPNA	0.56	0.41	0.51	0.88	0.54	0.16	0.02

For all associations, baseline values of the nutritional indices are used.
The QoL value is the correlation coefficient between the nutritional score at baseline and the mean of 13 QoL domains (see chapter 2.2).
Abbreviations: QoL = Quality of Life, HCS = Harrell's C Statistic, HL = Hosmer-Lemeshow Goodness-of-Fit test, CC = correlation coefficient, MIS = Malnutrition Inflammation Score, SGA = Subjective Global Assessment, cPENS = composite score on Protein-Energy Nutritional Status, GNRI = Geriatric Nutritional Risk Index, sAlb = serum albumin, sCr = serum creatinine, BMI = Body Mass Index, nPNA = normalized Protein Nitrogen Appearance

Future steps in PEW research

An ideal diagnostic test for PEW should be quick, easy, cheap, have an adequate association with the consequences of PEW, have a good intra- and interobserver reproducibility, change as a result of nutritional intervention and, obviously, this change should also be associated with improved clinical outcomes. Although the identification of the MIS out of the 8 investigated nutrition-related tests as the supposedly preferred method to assess PEW is an important step forward in this, still controversial, area, it is crucial to realize that multiple steps need to be taken before definitive answers will become available. Many nutrition-related scores, such as hand grip strength, mid-arm circumference muscle measurements, bioimpedance measurements or clinical scores have not been included in the investigations described in this thesis. Furthermore, some of the abovementioned properties of an ideal diagnostic test for PEW have not yet been investigated for every test. For example, it is presently unknown whether a deteriorating MIS is associated with clinical outcomes. Most urgently needed, however, are investigations with nutritional interventions and hard clinical outcomes. Although supplementation of glucose polymers,[44] essential amino acids,[45] a high-caloric and protein-rich diet,[46,47] a tailored approach to overcome nutritional barriers[48] and the use of biocompatible membranes[49] or ultrapure dialysis fluid[50] have been associated with improvements in nutritional indices in HD patients, only one RCT with hard clinical end points has been performed in this patient group. This study showed that intradialytic parenteral nutrition plus oral nutritional supplements does not result in an improved survival or less hospitalization when compared to solely oral nutritional supplementation.[51] Ideally, the aforementioned interventions will be investigated in a randomized setting, in which many nutritional indices are repetitively measured. A preferred score improves after such an intervention, and this beneficial effect should also induce better clinical outcomes. After determining the gold standard for PEW, easier tests can be investigated. A score with a fair relation with this gold standard may be a more convenient tool for clinical practice. In the meantime, it is important to be aware of the association between PEW and poor clinical outcomes. Patients supposedly suffering from this syndrome should be identified using multiple nutritional indices and treated according to nutritional guidelines,[16-19] while the evidence is awaited whether or not such interventions improve clinical outcomes.[52]

VASCULAR DAMAGE

Relevance of cardiovascular risk factors in HD patients

Nearly two decades ago, Foley and Parfrey reported on a 10- to 20 times higher cardiovascular risk for dialysis patients, compared to age-, sex- and race matched subjects from the general population.[53] Despite continuous research and increasing knowledge concerning the uremic syndrome, the mortality risk, of which a large part can be attributed to cardiovascular causes, remains alarmingly high in this patient group.[1,54] The underlying mechanisms of the high incidence and prevalence of cardiovascular complications in this specific population are complex and not yet fully understood.[55] Traditional cardiovascular risk factors, such as hypertension and a high cholesterol,[56] can only partly explain the high risk.[57] In this respect, it is interesting to note that treatment of hypercholesterolemia did not improve cardiovascular outcomes in this specific population.[58,59] Therefore, the contribution of non-traditional risk factors, such as chronic (micro)inflammation,[60] oxidative stress,[61,62] protein-energy wasting[63] and especially chronic kidney disease and mineral bone disorder (CKD-MBD),[64] is gaining increasing interest. The latter is characterized by disturbances in mineral and bone metabolism and/or extra-skeletal calcifications, particularly in the vascular system.[65] Only recently, both magnesium (Mg^{2+}, abbreviated Mg) and the glycoprotein sclerostin have been linked to this process.[66-68] In **chapter 3.1** and **chapter 3.2**, the relation of the serum levels of these markers with the clinical outcome in dialysis patients is described. Apart from vascular calcifications, an increase in the wall thickness of the myocardium, so called left ventricular hypertrophy (LVH), has been recognized as an independent cardiovascular risk factor in both the renal[69] and the non-renal population.[70] Currently, it is unknown whether different types of LVH have a dissimilar outcome in this population. Therefore, in **chapter 3.3**, clinical outcome was compared between patients with the eccentric and concentric type of LVH.

Findings

As described in **chapter 3.1**, an inverse relation was found between the concentration of serum Mg and all-cause and cardiovascular mortality as well as sudden death. Given the multiple papers reporting similar findings in various cohorts across the globe[67,68,71-73] and the extensive statistical correction for potential confounders in our analysis, this relation seems robust. In the study described in **chapter 3.2**, an inverse relation between the 22kDa-sized glycoprotein sclerostin and all-cause and cardiovascular mortality was found. Furthermore, from our analysis, it appeared that the serum sclerostin concentration remained stable in HD patients and decreased over time in subjects who were treated with HDF. Interestingly, this

decrease was positively related to the magnitude of the convection volume. Lastly, in **chapter 3.3**, the eccentric LVH type is identified as a risk factor for sudden death.

Future steps in this area

A number of key questions remain to be answered before these findings result in therapeutic options that may reduce the high mortality risk in this patient group.[1,53,54] Nonetheless, the identification of these as of yet unknown risk factors is an important first step. Crucial next steps are to establish causality and to find an intervention that is able to influence the determinant. Obviously, the intervention should improve clinical outcome. Furthermore, adverse effects must be carefully monitored during all research phases as such effects should not override supposed the beneficial effect(s). In addition, some other issues should be elucidated as well, but do not necessarily need to be clarified before an intervention can be implemented. For example, investigating subgroups may identify a certain type of patient that particularly benefits from the intervention. Furthermore, attention should be paid to the causal mechanisms of both clinical events and interventions, as new treatment strategies will definitely emerge in the near future. Lastly, in some cases, the cost-effectiveness of an intervention needs to be studied.

For Mg (**chapter 3.1**), the next step is to investigate whether its blood concentration can be influenced by increasing oral intake or by an elevation of the dialysate Mg concentration. Currently, a study is being prepared to investigate whether the latter intervention indeed results in a higher serum Mg. Importantly, proton pump inhibitor use, which is associated with hypomagnesaemia,[74,75] should be taken into account. Regarding the potential mechanisms of Mg, it is tempting to speculate about a role in heart rhythm stability given the relation of Mg with sudden death and the role of Mg in the de- and repolarisation of cardiomyocyte fluxes.[76]

In this respect, the relation between the type of LVH and sudden death, as described in **chapter 3.3,** justifies at least exploration of a possible interaction between left ventricular geometric patterns and Mg. The LV geometric pattern itself and its potential determinants, such as the role of fluid overload in the eccentric LVH (eLVH) type, should also be further explored. Whether the type of LVH changes over time and, if so, *how* it changes, are other highly interesting subjects for future research. Furthermore, it remains to be elucidated whether the implantation of an implantable cardioverter defibrillator (ICD) is warranted in this particular type of patient.

Returning to the possible mechanisms of Mg, other pathways may play a role in its relation with mortality as well. Mg appears to be involved in the glycaemic homeostasis[77] and has been inversely related to vascular calcification.[78,79] Possibly, part of the effect of Mg on vascular calcification can be explained through alterations in the activation of the Wnt pathway.[80] Sclerostin, the 22 kDa-sized glycoprotein studied in **chapter 3.2**, is a soluble inhibitor of this pathway. Thus, as Mg and sclerostin could be interrelated through this pathway, a possible interaction between these two factors and vascular calcification should be explored. Furthermore, given the complexity of bone alterations and the onset of extra-skeletal calcification in patients with advanced chronic kidney disease, the influence of other bone-related substances which may affect mortality, such as FGF23,[81] also warrants additional research. Indeed, some of these factors can be already influenced today and may thus alter the clinical course in these patients.[82] The effects of such interventions, however, remain to be determined. This also applies to the effect on clinical outcome of altering the serum sclerostin concentrations by dialysis modality as described in **chapter 3.2.**

In short, the studies described in this thesis are the first steps in exciting new research fields, which ultimately may lead to therapeutic options to improve the life expectation of dialysis patients.

POST-DILUTION ONLINE HEMODIAFILTRATION

Relevance of dialysis research

An estimated 3,2 million patients were treated for ESKD worldwide at the end of 2013.[83] This patient group suffers from various abnormalities that are associated with the uremic state, such as oxidative stress, PEW and chronic (micro)inflammation, resulting in an impaired QOL and an increased morbidity and mortality risk.[1-3,63,69] Such patients require renal replacement therapy (RRT), which can be subdivided into three groups: renal transplantation, extracorporeal treatments or peritoneal dialysis. Although transplantation is the preferred method of RRT as this treatment best restores the aforementioned abnormalities,[84-86] transplantation is only available to a small minority due to medical, logistical or economic reasons, especially in low- and middle income countries.[87] Moreover, the number of available donor kidneys is insufficient to transplant all ESKD patients. Quantitatively, only 678.000 ESKD patients (21%) lived with a renal transplant at the end of 2013; the remaining 2.522.000 patients (79%) depended on dialysis treatment, of which 89% was treated with a chronic intermittent extracorporeal treatment, i.e.

low-flux hemodialysis (HD), high-flux HD, hemofiltration or HDF.[83] It is noteworthy to mention that the prevalence of patients treated with RRT increases with 6-7% per year, versus a global population growth of approximately 1.1%.[83,87,88] Given the high societal and personal burden associated with ESKD and the benefits of transplantation over dialysis, prevention of ESKD and improved accessibility to transplantation are highly required. Furthermore, as a large proportion of ESKD patients is expected to remain dependent on an extracorporeal treatment and all parties involved aim for an optimal balance between an adequate dialysis treatment and QOL, continuous research in the field of dialysis is also necessary.

HDF and survival

The evidence concerning post-dilution online HDF is described in **chapter 4.1**. In short, HDF combines diffusion and convection to clear a larger spectrum of molecular weight toxins than HD, ranging from 0.5 to approximately 40 kDa.[89] Previously, the use of bags of sterile substitution fluid to correct for the excess of ultrafiltration (UF) on top of the interdialytic weight gain in HDF limited its use as this was economically and logistically inconvenient. The availability of large amounts of *online* produced sterile substitution fluid made it possible to perform HDF on a larger scale with higher substitution volumes.[90] Three large randomized controlled trials (RCTs) comparing post-dilution online HDF with conventional (i.e. low- or high-flux) HD were recently published. Two showed no difference in survival between the treatment arms (the Dutch CONvective TRAsport STudy [CONTRAST][91] and the Turkish ol-HDF Study [THDFS]).[92] The Catalonian study ESHOL, however, did show a survival benefit for patients treated with ol-HDF.[93] Importantly, the mean reached convection volume per session was the highest in this study (23.4L versus 19.8L in THDFS and 20.7L in CONTRAST). It should be mentioned, however, that both THDFS and ESHOL are limited by 'censoring alive' or 'informative censoring' (i.e. the censoring of patients due to other reasons than death or end of the study), resulting in fact in an 'on treatment' analysis, versus the preferred 'intention-to-treat' method that was used in CONTRAST. The first induces a problem when the events at which patients are censored other than death or end of the study are distributed unequally among the treatment arms. Furthermore, ESHOL excluded patients who did not reach 18L of convection volume per treatment on average, potentially introducing a selection bias. To overcome the methodological drawbacks, the results of the aforementioned three RCTs and a fourth, yet unpublished RCT, were pooled in an individual participant data analysis. In all studies, bias due to informative censoring was solved by actively pursuing the vital status of all included patients at the end of the concerning study. This enabled the possibility to perform an intention-to-treat analysis of post-dilution online HDF

versus HD in 2793 patients with 769 deaths and 292 cardiovascular deaths. From this analysis, it appeared that patients treated with HDF had a reduced mortality risk *per se* over subjects treated with HD (HR 0.86 [95% CI 0.75-0.99]). An even more pronounced reduction in the risk for cardiovascular mortality was found for patients treated with HDF compared to those treated with HD (HR 0.77 [95% CI 0.61-0.97]).[94]

Convection volume

Determinants

The convection volume (substitution volume plus net ultrafiltration [UF]) appears to play a key role in post-dilution online HDF. All three RCTs found an inverse relation between the magnitude of the convection volume and mortality in *post hoc* analyses, as was previously described in several observational studies.[95-98] The most important determinants of the convection volume are treatment-related rather than patient-related: treatment time, blood flow rate and filtration fraction.[99-101] As treatment time has also independently been associated with an improved survival,[102-104] the hypothesis was raised that the effect of the convection volume on survival may be the result of a longer treatment time in the high-volume group. However, by fitting various Cox regression models, it was shown that treatment time was not the driver of the inverse association between convection volume and mortality in the CONTRAST cohort (**chapter 4.2**).

Lower and upper threshold

Considering the aforementioned results, it seems important to detect the range of the convection volume associated with an improved survival. However, the lower threshold of 'high-volume HDF' varies across studies, as these boundaries are data driven rather than physiologically driven. In the three RCTs, a survival benefit was described in patients treated with HDF who reached a convection volume above 19.8L/session (THDFS), 21.95L/session (CONTRAST) or 23.1L/session (ESHOL)[91-93] on average. In *post hoc* analysis of the IPD study, it appeared that HDF patients who reached the highest convection volume on average, adjusted for body size (>23L/1.73m^2/session), had the largest survival benefit (adjusted HR for all-cause mortality 0.73 [95% CI 0.59-0.91] and adjusted HR for cardiovascular mortality 0.69 [95% CI 0.47-1.00]).[94] Recently, Canaud *et al* suggested in a restricted cubic spline analysis that patients treated with post-dilution online HDF that reach 55L/week of convection volume on average have a survival benefit when compared to HD, improving further up to 75L/week, which corresponds to 25L/treatment in a regular thrice-weekly schedule. Above this value, the survival decreases,

although data in this range should be interpreted with caution given the wide confidence interval.[105] Taking all data together, it appears that the survival benefit is unquestionably present above 22L of convection volume per treatment in a regular thrice-weekly schedule. The volume to obtain an optimal survival benefit seems approximately 25L/treatment, which is feasible in everyday clinical practice as is demonstrated in **chapter 4.4**. Considering body size, such uniform goals seem inappropriate. Intuitively, 25L/treatment in a 45 kg patient may have different effects than the same amount of convection volume in a 120 kg subject. Although neither the investigators of ESHOL nor Canaud *et al* found body composition to be significantly involved, this may be the result of a too homogenous population (i.e. only European patients) to demonstrate differences between different body composition for an equal amount of convection volume. Recently, it has been shown that unstandardized convection volume or convection volume standardized by body surface area or total body water was associated with a reduced mortality in the IPD analysis, whereas standardization by body weight or BMI was not.[106] Thus, future studies may need to take body size into account when investigating the effect of convection volume on mortality.

Achieving high volumes

As the three aforementioned determinants of convection volume (treatment time, blood flow and filtration fraction) are largely modifiable, it is important to explore technical and practical obstacles to obtain such volumes. These issues are described in **chapter 4.3**. As illustrated in this chapter, multiple factors may impact the magnitude of the convection volume, such as vascular access, needle size, the dialyser, hematocrit level and anticoagulation. Taking these aspects into consideration, a structured protocol was designed to optimize the determinants of the convection volume. In **chapter 4.4**, is it described that using this stepwise approach, high-volume HDF, arbitrarily considered a convection volume ≥22L/session, is feasible in the vast majority of ESKD patients (80%). This confirms the former finding that the magnitude of the convection volume is mainly determined by center policy rather than by patient factors.[100] Importantly, the mean reached convection volume per session was approximately 26L/session.

Mechanisms driving the effect of HDF

Assuming causality in the inverse relation between the magnitude of the convection volume and mortality in HDF irrevocably raises the question of the possible mechanism(s) involved. In this respect, it is noteworthy to mention that the survival advantage of high-volume HDF is almost exclusively due to a reduction in cardiovascular mortality.[94,107] The hypothesis of an enhanced clearance of MMW uremic

toxins, thus reducing uraemia in ESKD patients, is appealing, although no single solute has yet been identified that explains the effect. On the other hand, this possibility cannot be excluded as many MMW substances are yet to be identified. This is illustrated by the finding of a reduction in serum sclerostin, a 22kDa-sized glycoprotein, over time in patients treated with HDF, whereas the sclerostin concentration remains stable in patients treated with HD (**chapter 3.2)**. Of note, the effect of the enhanced clearance of sclerostin by HDF on clinical outcomes remains to be determined. Furthermore, the removal of the phosphate-regulating protein FGF-23 by HDF,[82] which has been associated with mortality,[108] appears a promising candidate to support the aforementioned hypothesis. Additional research is warranted to further explore this thought. Another possible mechanism behind the effect of high-volume HDF is a better intra-dialytic hemodynamic stability. Intradialytic hypotensive (IDH) periods may lead to intermittent hypoperfusion of the brain, gut and heart during dialysis.[109-111] In pre-dilution HDF, a reduced number of these periods has been described when compared to HD.[112] Interestingly, treatment with cooled dialysis fluid has also been associated with a reduction in IDH periods and brain injury, slower progression of HD-induced cardiomyopathy and improved cardiovascular survival.[111,113,114] As a small sample size randomized cross-over trial found an association between a prolonged treatment and improved hemodynamic stability, irrespective of the dialysis modality used (i.e. HD or post-dilution online HDF, both with cooled dialysate),[115] the cooled dialysate may at least partly explain the effect in the study by Locatelli *et al*.[112] However, importantly, the mean substitution volume was only 14.1L per HDF treatment in the study from Cornelis *et al*.[115] Thus, it appears that the effect of HDF on IDH may result from cooling, which is obviously most pronounced when high convection volumes are applied. Third, ESKD has been related to structural damage of the left ventricle, inducing an increased risk in all-cause and cardiovascular mortality as well as in sudden death (**chapter 3.3**). It has been suggested that the deterioration in damage of the left ventricle is reduced or null in patients treated with HDF,[116] which, however, could also be the result of one or both of the abovementioned hypotheses. Lastly, an additive or multiplicative effect of these hypotheses also appears possible.

Safety and drawbacks of HDF

Microbiological safety is an important issue in HDF given the infusion of >20L of substitution fluid per treatment. However, tens of thousands if not hundreds of thousands HDF treatments have been performed safely in the last decades.[117-120] In fact, the switch from conventional dialysis fluid to ultrapure dialysis fluid has been associated with improvements in CRP and IL-6.[50,117,121] Furthermore, as mentioned above, some studies suggest a beneficial effect of treatment with HDF

on inflammatory markers,[122,123] whereas others report similar levels.[98] As no study suggests a disadvantageous inflammatory effect of HDF, this treatment modality is considered safe and well tolerated. Given the high UF rate in HDF compared to HD, the trans-membrane pressure (TMP) increases with the convection volume and during dialysis, as is described in **chapter 4.4**, inducing an enhanced platelet activation.[124] Whether this effect is detrimental, however, remains to be determined. It is noteworthy that the pressures reached in the high-volume HDF feasibility study (**chapter 4.4**) are indeed approximately 60% higher at the end of the optimization protocol than at the start of the study. However, only few reached a TMP over 400 mmHg, which was considered the safety threshold, and only at the end of the dialysis session. Furthermore, due to the rising hemoconcentration in the dialyser as a result of the high UF rate, a higher dose of anticoagulation is necessary to prevent clotting.[125] The impact of this finding, however, has not yet been investigated. Conflicting results exists as to whether HDF induces a decline in serum albumin.[92,93,126] In addition, treatment with HDF has been associated with an increased loss of vitamin C.[127] Lastly, an unwanted loss of (other) essential metabolic elements due to the increased clearance of MMW elements appears plausible. Nevertheless, as no study provided evidence for HDF as an *inferior* treatment when compared to HD with respect to survival and various studies show beneficial effects of treatment with HDF, the benefits of this treatment modality appear to override its drawbacks.

Current clinical practice

The three aforementioned RCTs and the observational studies on HDF[91-93,95-98] have several methodological drawbacks, as already described. Furthermore, several meta-analyses on aggregated data report heterogeneous results on convective treatment versus diffusive treatment due to differences in the type of treatment included in the convective treatment arm,[128-132] which appears inappropriate,[133] as is described in **chapter 4.1.** The recent results of the IPD analysis show a survival benefit for patients treated with post-dilution online HDF *per se.* Importantly, the additional costs of HDF over high-flux HD, which is currently considered the first choice treatment in many cases and for which ultrapure dialysis fluid is necessary, seem minimal as the only difference is an extra line. Therefore, it seems time for a paradigm shift to post-dilution online HDF as a first choice treatment for patients undergoing thrice-weekly in-center chronic intermittent extracorporeal dialysis treatment.[134] As such and considering all evidence, the current guidelines seem outdated. Neither the 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) guideline on hemodialysis adequacy, peritoneal dialysis adequacy and vascular access,[135] nor the 2007 European Best Practice Guideline (EBPG) on dialysis strate-

gies,[136] nor the 2009 British Renal Association Haemodialysis guideline[137] included the three large RCTs comparing post-dilution ol-HDF with HD, let alone the IPD analysis. Also, these guidelines do not comprehend the recent insights concerning the potential importance of the convection volume. Rather, all guidelines recommend to dose the adequacy of all extracorporeal treatments by Kt/V, including HDF. Fortunately, a more recent consensus statement from the EUropean DIALysis working group (EUDIAL) of the ERA-EDTA indicates that at least in Europe, the focus is shifting to HDF.[138] In short, updated HD guidelines are warranted that consider HDF as the preferable chronic intermittent dialysis treatment with beneficial effects over conventional thrice-weekly HD, of which the dose should be based on the magnitude of the convection volume.

Future HDF research

The feasibility of high-volume HDF in the vast majority of ESKD patients as described in **chapter 4.4** is an important step forward in HDF research and paves the way for a trial comparing different convection volumes in a randomized setting to definitively confirm or refute a dose-response relation between the magnitude of the convection volume and survival. Furthermore, the mechanism(s) behind the potential effect of HDF warrant clarification, as do the drawbacks of this treatment. Lastly, the effect of intensified HDF treatments, such as short-daily or nocturnal HDF,[139] and the role of HDF in paediatric dialysis remains to be elucidated.

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