Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Dialysis, derived from the ancient greek word διάλυσις (separation), was used for the first time in 1861 by the Scottish chemist and medical doctor Thomas Graham to describe the "method of separation by diffusion through a septum of gelatinous matter".[1] His findings about osmotic forces through a semi-permeable membrane are still the basis of modern hemodialysis (HD) treatment.[1,2] Yet, it took more than half a century before the first HD session was demonstrated in a rabbit,[3] and still fifty years later before the Dutch physician Willem Kolff first successfully treated a patient suffering from the hepatorenal syndrome with the 'rotating drum kidney' in 1945 and thus saved her life.[4] Only after the development of commercially produced cellulosic based membranes, heparin and the external Teflon-silastic shunt by Quinton and Scribner in 1961, HD became available as a life-prolonging treatment for patients suffering from end-stage kidney disease (ESKD).[5,6] Clyde S., the first patient on chronic dialysis, lived with this treatment for 11 years.[7]

Due to considerable improvements in membrane technology and water treatment systems, the creation of an internal arterio-venous fistula and the development of commercially available anticoagulation, HD is currently a routine treatment in developed countries for patients with ESKD.[8] At the end of 2013, approximately 2.250.000 patients were treated with chronic intermittent HD worldwide.[9]

Despite these developments and considerable progress in the medical knowledge of the uremic state in recent decades, both life expectancy and quality of life remain severely impaired in HD patients.[10-13] Actually, as renal replacement therapy (RRT) with a dialyzer is completely different from the physiologic function of native kidneys including its hormonal activity, standard HD is far from ideal to resolve the multiple abnormalities that have been described in uremic patients, such as a (micro)inflammatory state, anemia, chronic kidney disease - mineral bone disease (CKD-MBD) and protein-energy wasting (PEW).

In an attempt to overcome these restrictions the best way possible, large pore dialysers were developed. These can be used either in a more efficient HD technique (high-flux HD) or in a rather different dialysis modality called hemodiafiltration (HDF). Both techniques combine the diffusive capacity of standard HD for small molecules, such as urea (80 Da) with some (high-flux HD) or a considerable (HDF) capability to remove larger molecules, including β2-microglobulin (12 kDa), by convection.

OUTLINE OF THIS THESIS

The present thesis focuses on three aspects within this patient group. First, how to assess protein-energy wasting (PEW). Second, to describe the association between various cardiovascular risk factors and mortality. Third, to describe the role of the convection volume in the clinical outcome of patients who are treated with post-dilution online HDF.

PROTEIN-ENERGY WASTING

Although introduced earlier, the term PEW was used in 2008 by the International Society of Renal Nutrition and Metabolism (ISRNM) to define the state of decreased body stores of protein and energy fuels.[14] Etiologically, insufficient food intake, increased resting energy expenditure, inflammation, acidosis, endocrine disorders and the dialysis procedure itself may be involved.[15] The expert panel of the ISRNM stated that PEW is present if 3 out of 4 diagnostic criteria are abnormal: (1) serum chemistry (low serum albumin, pre-albumin or cholesterol), (2) body mass (low BMI, unintentional weight loss or low body fat percentage), (3) muscle mass (muscle wasting, reduced mid-arm circumference or creatinine appearance) and (4) dietary intake (unintentional low protein or energy intake).[14] It has to be noted, however, that these diagnostic criteria are 'expert opinion' based and therefore prone to bias.[16] Currently, PEW lacks a gold standard, as is indicated by the wide variety of clinical nutritional scoring lists, self-assessment tools and measurements by bioelectrical impedance and blood chemistry used for this purpose.[17,18]

Most nutrition-related score systems indicate that PEW is highly prevalent among HD patients[19-21] and associated with increased mortality, vascular calcification, hospitalization and a decreased quality of life.[14] As patients suffering from this syndrome may benefit from protein or energy supplementation, it seems important to define and detect PEW accurately.[22-24] Therefore, in the first part of this thesis, the association between various clinical nutritional screening tools and a number of outcome parameters are compared.

CARDIOVASCULAR RISK FACTORS

A large proportion of deaths in HD patients can be attributed to cardiovascular causes.[25] The etiology of the extremely high cardiovascular risk among this patient

group is complex and has been attributed to both patient- and treatment-related aspects. With respect to the latter, the bio-incompatibility of the extra-corporeal circuit as well as the repeated administration of heparin for several months or even years, may harm the patients. Considering patient-related factors, the detrimental effects of both traditional risk factors, such as hypertension and diabetes, and non-traditional risk factors, such as chronic (micro)inflammation, oxidative stress, chronic kidney disease – mineral and bone disease (CKD-MBD) and fluid overload, may play a role.[26-28] CKD-MBD is characterized by abnormalities in bone turnover, extraskeletal calcifications and abnormalities in mineral metabolism such as PTH, calcium, phosphorus and FGF-23.[29,30] Recently, it has been suggested that both magnesium and sclerostin may be involved in CKD-MBD and play a role in the high cardiovascular risk among these patients.[31-33] Another abnormality that is commonly seen in HD patients (70%) is left ventricular hypertrophy, which is also recognized as an independent cardiovascular risk factor in these patients.[34] Therefore, the second aim of this thesis is to investigate the association between mortality and a variety of cardiovascular risk factors, including the biomarkers magnesium and sclerostin, the left ventricular geometric pattern and the dialysis modality used (HDF versus HD, see below).

POST-DILUTION ONLINE HEMODIAFILTRATION

Although HD is a life-prolonging treatment in ESKD patients, their clinical outcome remains poor.[10,12] As mentioned above, conventional HD with low-flux dialysers is an adequate method to clear small uremic (low molecular weight [LMW]) substances such as urea by diffusion. However, simply increasing the dialysis dose as measured for urea by the formula eKt/V_{urea}, did not result in an improved outcome.[35] In addition, the mere replacement of low-flux dialysers by high-flux devices, which remove some larger substances as well, did not improve the high mortality risk in HD patients either.[35-37]

To increase the amount of convective transport, HDF was suggested as an alternative dialysis modality some decades ago (figure 1). In HDF, a large amount of plasma water is extracted from the patient on top of the desired ultrafiltration (UF) to correct for the interdialytic weight gain. In modern HDF, the 'extra' UF is replaced by *online* produced sterile substitution fluid, which can be administered before (pre-dilution), after (post-dilution), midway (mid-dilution) or before and after (mixed-dilution) the dialyser (figure 2). As post-dilution online HDF (HDF) removes uremic solutes most effectively,[38] this seems the preferred site of substitu-

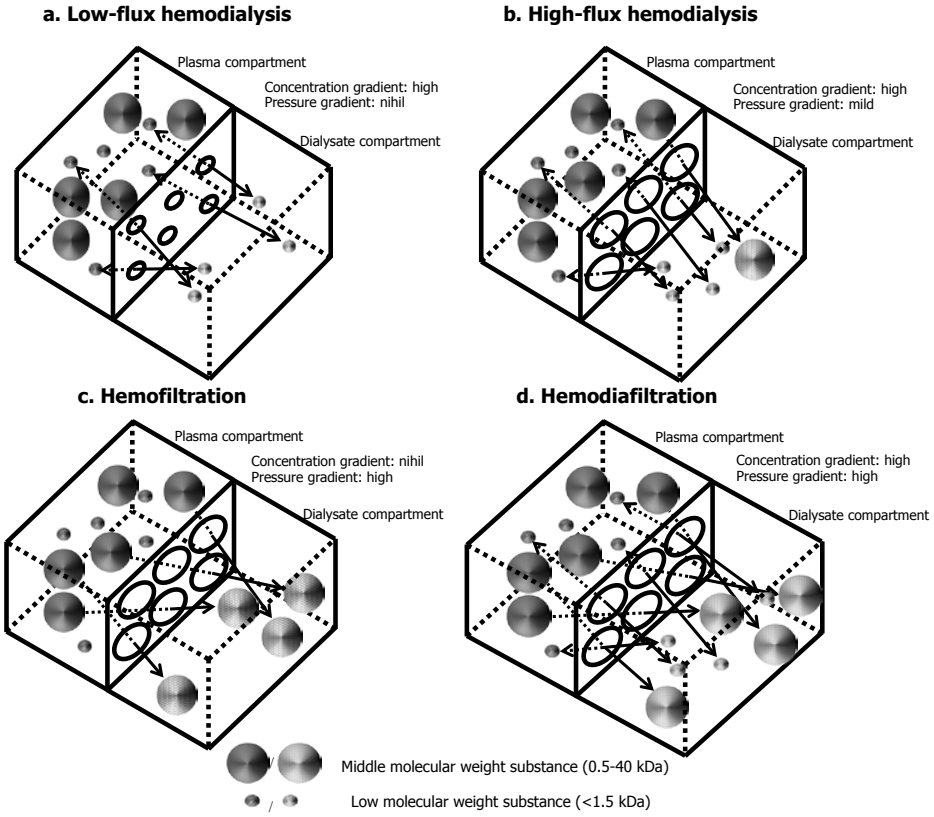

Figure 1. Schematic overview of various hemodialysis modalities.

tion. Geographically, HDF is mainly used in Europe and Japan. Due to problems with regulatory authorities, HDF is only performed on a limited scale in the US.

Recently, three large randomized controlled trials (RCTs) were published comparing HDF and HD. Two of these, the Dutch CONvective TRAnsport STudy (CONTRAST)[39] and the Turkish ol-HDF Study (THDFS)[40] did not found a difference in survival between the two treatment arms in primary analysis. The third, however, the Catalonian Estudio de Supervivencia de Hemodiafiltración On-Line (ESHOL), in which the highest convection volumes on average were achieved (mean volume/session 23.4L versus 20.7L in CONTRAST and 19.8L in THDFS), did find a markedly survival advantage of HDF (HR 0.70; 95% CI 0.53-0.92).[41] A recent individual participant data (IPD) analysis on the three RCTs plus an unpublished fourth showed a significant better survival for patients treated with HDF over subjects treated with HD (HR 0.86; 95% CI 0.75-0.99).[42] Furthermore, all three RCTs and the IPD analysis showed an inverse relation between the magnitude of the convection volume and

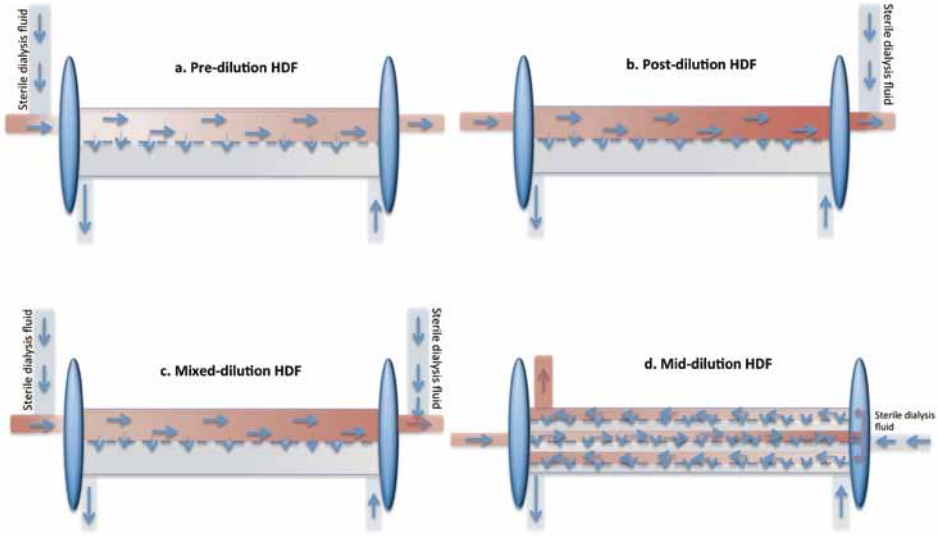

Figure 2. Overview of the possible sites of infusion of sterile fluid in HDF.

mortality in *post hoc* analyses, which is in line with findings from several observational studies.[43-46] As all available evidence points in one direction, it appears legitimate to consider the convection volume as the dose of HDF, which is the subject of the third part of this thesis.

SUMMARY

HD patients face a wide variety of complications, both due to the uremic state and treatment-related factors. In this thesis, the following items are addressed:

1. How to assess PEW in patients with ESKD? Various clinical nutrition-related scoring tools are compared by investigating their relationship with different clinical outcome parameters.
2. What is the relation between mortality and cardiovascular risk factors, such as magnesium, sclerostin and the left ventricular geometric pattern in patients with ESKD?
3. What is the role of the convection volume with regard to the possible survival benefit of post-dilution online HDF and how can we optimize its magnitude in patients with ESKD?

The thesis concludes with a general discussion and a summary of the findings.

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