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On-Line Hemodiafiltration in the Large RISCAVID Study

Vincenzo Panichi[a] · Ciro Tetta[b]

[a]Nephrology and Dialysis Versilia Hospital, Versilia, Italy; [b]Fresenius Medical Care, Bad Homburg, Germany

Abstract

Despite significant advances in hemodialysis (HD) and medical therapy, mortality rates in patients with chronic kidney disease stage 5 (CKD-5D) remain unacceptably high, with cardiovascular (CV) mortality risk in dialysis patients being several times higher than that of a general population. The CV mortality risk of a 25- to 34-year-old dialysis patient is approximately the same as the one of an otherwise healthy person aged over 85 in the general population. HD patients are not only exposed to the various traditional risk factors valid for the general population but in addition also to the non-traditional risk factors resulting either from uremia per se or from the dialysis treatment. Our understanding of chronic inflammation in CKD-5D and of its influence in the accelerated atherosclerotic process has greatly evolved. Dialysis therapy, performed efficiently, has the potential to provide CKD-5D patients with benefits beyond the life-saving function of removal accumulated waste products and excess fluid. There is sufficient evidence to indicate that on-line hemodiafiltration has the potential to improve chronic inflammation, fluid overload, left ventricular hypertrophy, anemia and quality of life of CKD-5D patients. In the search for more effective, safer and less expensive approaches to the management of the above conditions, an innovative concept of biocompatibility should be broadened to the HD system/patient evaluation. Here, we intend to present new insights obtained from a prospective observational study (RISCAVID, 'RISchio CArdiovascolare nei pazienti afferenti all'Area Vasta In Dialisi') performed on a large HD population in the northwestern region of Tuscany, Italy, on the assessment of the different parameters of chronic inflammation and gross/CV mortality and anemia management.

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The concept that inflammation underlies many diseases, once considered to be linked to degenerative processes, has revolutionized the approach to the research into the pathogenesis and new therapeutics alike. In the field

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of cardiovascular disease (CVD), the process of endothelial dysfunction, vascular damage and atherosclerosis is now seen as a continuum [1]. CVD is among the leading causes of morbidity and mortality in chronic kidney disease stage 5 (CKD-5D) patients on maintenance hemodialysis (HD) [2, 3]. Even patients with reducing renal function already present with signs of chronic inflammation. Once patients are on HD, the risk of cardiovascular (CV) death is approximately 30 times higher than in the general population, and still remains 10–20 times higher after stratification for age, gender, and presence of diabetes. It is now well established that inflammation plays a primary role in arterial damage in HD patients [4, 5]. Although the precise mechanisms that are responsible for inflammation in ESRD are still unclear, the uremic status per se, low-grade infection, repeated exposure to foreign surfaces and auto-oxidation products are considered as likely inciting factors in these patients [6]. Recent studies have shown that epigenetic modifications orchestrate the epithelial-mesenchymal transition and eventually fibrosis of the renal tissue. Oxidative stress, inflammation, hyperhomocysteinemia, and uremic toxins could induce epimutations in CKD. Epigenetic alterations are associated with inflammation and CVD in patients with CKD [7]. Furthermore, a variety of traditional and non-traditional risk factors such as sympathetic hyperactivity, dyslipidemia, hyperphosphatemia/hyperparathyroidism, diabetes, and smoking may activate and/or amplify the inflammatory process in CKD-5D.

Inflammatory mechanisms play a relevant role in the development and progression of atherosclerosis [8] and heart failure [9]. Epidemiological studies in the general population have shown that even minor elevations of C-reactive protein (CRP), an acute-phase reactant that markedly increases during an inflammatory response [10], predict the development of coronary heart disease and cardiac failure [11–13]. CRP may directly promote the development of atherosclerosis, through complement activation, tissue damage and activation of endothelial cells. Studies performed in CKD-5D patients showed that CRP is a strong predictor of CV death [14, 15]. The link between CRP and CV risk was initially thought to be indirect, reflecting circulating CRP only to the extent of the acute phase reaction in response to non-specific stimuli such as confounding risk factors, atherosclerosis, vascular injury, ischemia and necrosis. However, several arguments now indicate that CRP is not merely an epiphenomenon, but it is also involved in the pathogenesis of the disease.

Stenvinkel et al. [16] first convincingly showed that the malnutrition-inflammation-atherosclerosis (MIA) syndrome is associated with the highest mortality rates in CKD-5D. Their results have been confirmed and extended [17]. As reviewed by Stenvinkel and Bárány [18], there is consensus on a link between CKD-5D and inflammation. A number of studies have highlighted the association between increased inflammatory indexes and a reduced response to erythropoiesis-stimulating agents (ESAs), in particular, high CRP levels were

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found in HD patients requiring higher ESA doses [19, 20]. However, the association between ESA resistance and increased CRP levels [21] is still unclear. Plasma interleukin (IL)-6 rather than CRP seems to better predict outcomes in CKD-5D patients [22]. Various possible explanations may underline the advantage of IL-6 over CRP as a predictor of ESA resistance. One possibility is that IL-6, being located upstream in the cascade of events which lead to the synthesis of many acute-phase reactants, is a better marker for the inflammatory burden affecting the development of CVD [23]. A frequently-asked question is what is the contribution of HD bioincompatibility to the chronic inflammatory state? In this context, the evolution of HD technology has moved the focus from membrane bioincompatibility only to a more complex and integrated view of the HD system. The possibility that HD may be shift to a 'cardioprotective" therapy is inherent to new technologies in machines, water treatment, dialysis fluids and blood tubings.

Originally introduced as an elegant concept in 1986 [24], the 'interleukin hypothesis' was first coined to indicate the production of IL-1, the endogenous pyrogen as produced by the result of complement-activated mononuclear cells. Indeed, the interleukin hypothesis explained much more than was initially predictable. Ever since, several studies have reported an increased cytokine production secondary to blood interaction with contaminated dialysate. IL-1, tumor necrosis factor-α and mainly IL-6 are the three pro-inflammatory cytokines that are involved in the pathogenesis of HD-dependent chronic inflammation [as reviewed in 25, 26].

The proposed mechanisms include blood interaction with endotoxins from the contaminated dialysate through HD membranes. A large number of studies have greatly contributed to increasing our knowledge in the mechanisms of endotoxin transfer across the membranes. In fact, when using high permeability membranes, backfiltration and backdiffusion occur [27]. Thus, the transmembrane passage of endotoxins or other cytokine-stimulating substances occurs during HD [28]. The reduction of backfiltration of standard dialysate may reduce the plasma concentration of IL-1ra, a sensitive indicator of inflammation in HD patients [Dinarello, pers. commun., 2004], and IL-1 [17]. Studies on large groups of patients have shown that high-volume exchange hemodiafiltration (HDF), a modality in which dialysate backfiltration is minimal, is associated with significantly lower CRP plasma values [17]. Comparing in a double crossover study patients treated with high-flux and on-line HDF using ultrapure dialysate and infusate, it was shown that a significant reduction of pro-inflammatory CD14+/CD16+ mononuclear subset occurs in on-line HDF [29]. These studies emphasize that the convective component has an additional anti-inflammatory effect [30].

The new technology of pyrogen-adsorbing, non-complement activating, high-permeability synthetic membranes and dedicated machines [31], as well as the awareness of the deleterious effects derived from

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contamination of dialysis fluids, has reduced the clinical impact to a periodic microinflammatory stimulus. Undoubtedly, the availability of monitors for on-line HDF and its increased popularity have spurred more restrictive measures on safety issues and monitoring. Water quality is a mandatory issue. Nowadays, the consolidated, clinical experience with on-line HDF warrants well-defined procedures and leaves no space for 'experiments' in what is now routine [32, 33]. The 'hemocompatibility network' should eventually prevent the periodic microinflammation induction through the implementation of rigid protocols of disinfection and maintenance of water treatment systems and HD monitors [3].

Experience of the RISCAVID

In June 2004, a prospective observational study (RISCAVID, *'RISchio CArdiovascolare nei pazienti afferenti all'Area Vasta In Dialisi'*) was started with the aim to investigate the link between traditional and non-traditional risk factors on mortality and morbidity in a large and homogenous HD population in the northwestern region of Tuscany. 757 patients representing the whole HD population of 1,235,062 inhabitants were included. Each of the 15 dialysis facilities of this region provided at the start of the study blood samples from all patients for the determination of inflammatory markers and at the start and every 6 months data on patients' demographic characteristics, renal history, laboratory values, comorbid disease, dialysis techniques, vascular access prescriptions and outcomes (table 1).

Three papers have been published to date on the basis of the results of the RISCAVID database. The first described the role of chronic inflammation and the impact of different HD modalities on morbidity and mortality rates [34]. The second focused on the erythropoietic response to ESA treatment and the factors involved in resistance to ESA [23]. The third examined the clinical relevance of serum mineral derangements, and the impact of different therapeutic strategies on mineral metabolism and mortality [35].

Chronic Inflammation and the Impact of Different HD Modalities on Morbidity and Mortality

High levels of CRP and inflammatory cytokines and low serum albumin are strong outcome predictors in CKD-5D patients, supporting the hypothesis that chronic inflammation is an important risk factor for CV and overall mortality in this population. CRP, IL-6, IL-8 and albumin have synergic effects on CV and overall mortality. In practical terms, determination of CRP at least at the initiation of HD might be recommended to evaluate an increased

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Table 1. Population, clinical and laboratory characteristics as well as HD modalities

Demographics and clinical characteristics (757 patients)	
Age, years	66 (14)
Male/female	458/296
Dialytic age, months	70 (76)
Body mass index	23.9 (4.4)
Comorbidites	
CVD	197 (26%)
Diabetes	143 (19%)
Hypertension	265 (35%)
Malignancy	106 (14%)
Systolic BP, mm Hg	135 (21)
Diastolic BP, mm Hg	74 (10)
HD modalities and parameters	
HD modalities, n (%)	
BHD/Kt/V	424 (56%)/1.39
HDF/Kt/V	205 (27%)/1.41
On-line HDF/kT/V	128 (17%)/1.43
Type of membrane, n (%)	
Modified cellulose	98 (13%)
Synthetic	659 (87%)
Laboratory parameters	
Hemoglobin, g/dl	11.6 (1.5)
Iron, µg/dl	70.4 (36)
Transferrin, mg/dl	179.9 (48.7)
Ferritin, ng/dl	496.4 (523)
TSAT, %	29.4 (17)
ERI, IU weekly/kg/g hemoglobin	11.9 (9.3)
Patients receiving ESAs, n (%)	651 (86%)
Calcium, mg/dl	9.1 (3.2)
Phosphate, mg/dl	4.8 (1.5)
iPTH, pg/dl	277 (282)
Ca × P, mg^2/dl^2	44.4 (14.8)
Total serum cholesterol, mg/dl	169.3 (47)
LDL cholesterol, mg/dl	88.9 (38.6)
Albumin, g/dl	3.7 (0.4)
CRP, mg/dl	10 (14.5)

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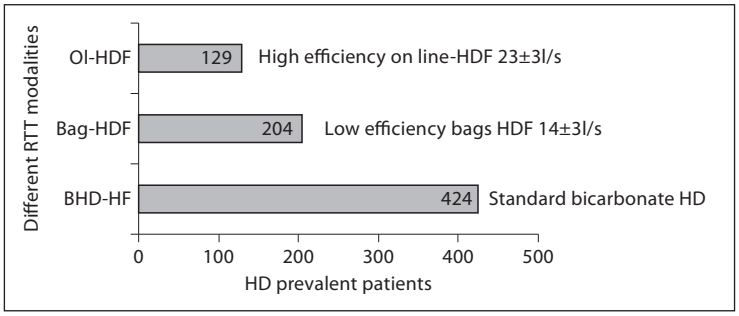

Fig. 1. RISCAVID study population according to dialysis technique.

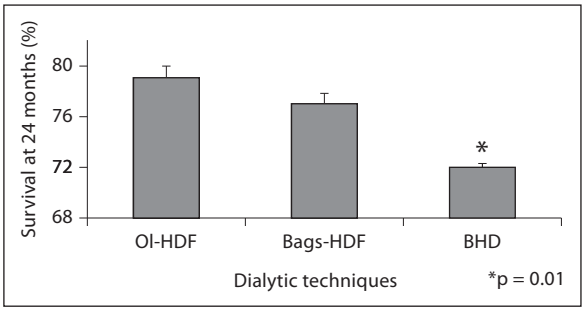

Fig. 2. Cumulative survival of patients receiving bicarbonate dialysis in comparison to patients receiving bags of HDF and on-line HDF.

risk and to appropriately adjust patient medication and care. Our study also provided information on the effect of different HD modalities on chronic inflammation and consequently on the cumulative survival. IL-6, a strong predictor for CV mortality, was found to be decreased in on-line HDF. The enhanced cumulative survival of patients receiving HDF in comparison to standard bicarbonate dialysis observed in RISCAVID (fig. 1, 2) extended the results by Canaud et al. [36] who compared the mortality of patients receiving HDF to that of patients receiving HD in a large cohort prospectively followed for 3 years in the Dialysis Outcomes and Practice Patterns Study (DOPPS) [37]. These authors showed that the mortality risk of patients receiving high-efficiency HDF was significantly lower (35%) when adjusting for differences in the comorbidity profile. However, in the DOPPS only surrogate markers of inflammation were measured, i.e. albumin and ferritin, since the measurements of CRP and cytokines had originally not been taken into account in the data collection. With respect to the DOPPS, the RISCAVID population differed from other existing studies in the high incidence of mixed convective-diffusive techniques (HDF 44% of the entire population). Of interest in our

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study, the difference in cumulative survival started after 15 months of observation after adjustment for age, dialysis vintage and comorbidities. At variance with the paper with Canaud et al. [36], we were not able to establish a relationship between mortality and volume exchange. Despite this limitation, HDF using sterile bags is customarily prescribed using 10–15 liters/session of reinfusion fluid while on-line HDF is performed with at least 22–25 liters/session.

EPO Resistance

Using the RISCAVID database, we investigated how anemia, ESA resistance and the plasma levels of biological markers of chronic inflammation could influence all-cause mortality and fatal/non-fatal CV events. Anemia is a common complication and predictor of mortality in CKD-5D patients [38]. A vast majority of these patients receives ESAs and resistance to this therapy is common [39]. In CKD-5D patients, anemia is linked to inflammation and oxidative stress is associated with the uremic syndrome [18]. Moreover, CKD-5D patients may require much higher than usual doses of ESAs in order to maintain the recommended hemoglobin target of ≥11 g/dl [40]. In many instances, these patients will have either an obvious or a clinically unapparent inflammatory process to account for the hyporesponsiveness to ESA replacement therapy. In this setting, the term ESA resistance has been introduced to define patients who fail to reach the target despite a higher than usual dose of ESAs or who continuously need higher doses in order to maintain it. Firstly, hemoglobin levels <11 g/dl were associated with the highest risk for all-cause mortality and fatal/non-fatal CV events while patients with hemoglobin levels >11 g/dl had the lowest all-cause mortality risk which was comparable to the reference group (no ESAs). After adjusting for confounders, hemoglobin did not affect fatal/non-fatal CV events. Other factors such as age, history of CVD, and serum albumin influenced both all-cause mortality and fatal/non-fatal CV events; CRP was a predictor of all-cause mortality but not of fatal/non-fatal CV events; conversely total cholesterol predicted fatal/non-fatal CV events but not all-cause mortality. Of note, Kt/V, pre-HD blood urea, HD vs. HDF, smoking and pulse pressure increased the relative risk of all-cause mortality and/or of fatal/non-fatal CV events at the univariate but not at the multivariate analysis. Moreover, CRP and IL-6 did not increase the relative risk of fatal/non-fatal CV events. Furthermore, the degree of ESA resistance showed a highly significant correlation with all-cause and CV mortality. In our model, the predictive power of the degree of resistance was higher than that of hemoglobin. Moreover, hyporesponders were the oldest and had the lowest serum albumin and TSAT levels as well as the highest plasma IL-6 values. However, serum albumin is not a valid marker of protein energy wasting

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given its dependence on inflammation, urinary albumin losses and hydration status. Finally, factors that influenced the degree of ESA resistance were low serum albumin, IL-6, as well as TSAT and therapy with sevelamer, statins and ESA. Of note, CRP did not influence the ESA Resistance Index (ERI).

Although the study was confirmatory, the results are based on a rather large cohort of a rather homogenous HD population. The prognostic significance of resistance to ESAs has been studied before by Kilpatrick et al. [41], who showed that a greater responsiveness to ESAs is associated with improved survival. As shown by the secondary analysis of the CHOIR trial [42], patients achieving their hemoglobin target had better outcomes than those who did not. Therefore, the evaluation of the mechanisms interfering with the action of ESAs seems relevant for the determination of an appropriate anemia management.

Impact of Mineral Metabolism Derangements

In a third paper, the impact of phosphate, calcium, intact parathyroid hormone (iPTH), K/DOQI recommendations, and different therapeutic strategies for chronic kidney disease-mineral bone disorders (CKD-MBD) on CV and all-cause mortality in the RISCAVID population was reported. At study entry, according to K/DOQI guidelines, only 71 (9%) and 239 (32%) patients exhibited all four or at least three bone mineral parameters (namely Ca, Pi, Ca × Pi and iPTH) within the suggested ranges. Despite a similar prevalence, the severity of CKD-MBD appeared different to what was reported in the USA. Of interest, none of the serum biomarkers or the number of serum biomarkers within K/DOQI targets were independently associated with all-cause and CV mortality. When Pi, calcium phosphate and all-cause and CV mortality were plotted together, a U-shaped relationship was noted for both parameters (fig. 3, 4). However, adjustments for factors calcium phosphate product with Pi and calcium phosphate significantly attenuated these associations that lost statistical significance. Similar to that found by others, the CKD-MBD syndrome affects the majority calcium phosphate product of patients enrolled in the RISCAVID study. Nonetheless, though our findings are in line with what was reported in the Italian cohort of the DOPPS study, a few differences deserve consideration. When compared to the overall DOPPS study cohort, hyperphosphatemia and the use of phosphate binders is substantially less prevalent in the RISCAVID study [43, 44]. However, the lower prevalence of hyperphosphatemia might be partly accounted for by differences in race, diet, dialysis and CKD-MBD management that exist between countries. Indeed, some authors suggested women and Blacks tend to have higher levels of serum phosphate, iPTH and FGF-23. Furthermore, the greater use of convective/diffusive techniques in our study, the low-protein diet and different nutrition policies might also contribute to the low prevalence of hyperphosphatemia in Italy.

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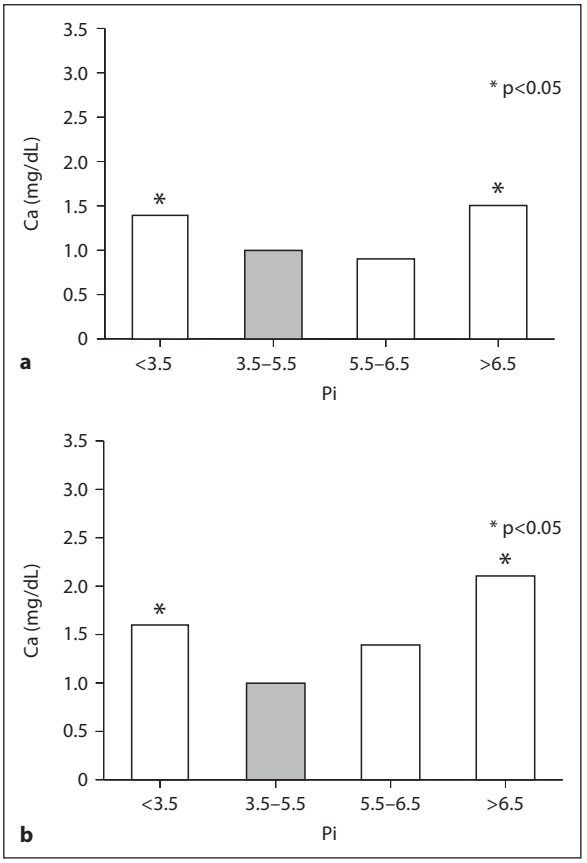

Fig. 3. Overall (**a**) and CV (**b**) mortality relative risk according to phosphate levels.

Conclusions

The RISCAVID database with both an incident and prevalent population homogenous for origin and similar practice patterns has proved to be a relevant tool for following up a large cohort over 36 months and for drawing and conclusions on the incidence and evolution of chronically inflamed patients regarding morbidity and mortality. The impact of chronic inflammation on ESA resistance has also been shown. Despite the limitations inherent to any observational study, we are continuing to accrue data on this geographical region to further extend our observations period.

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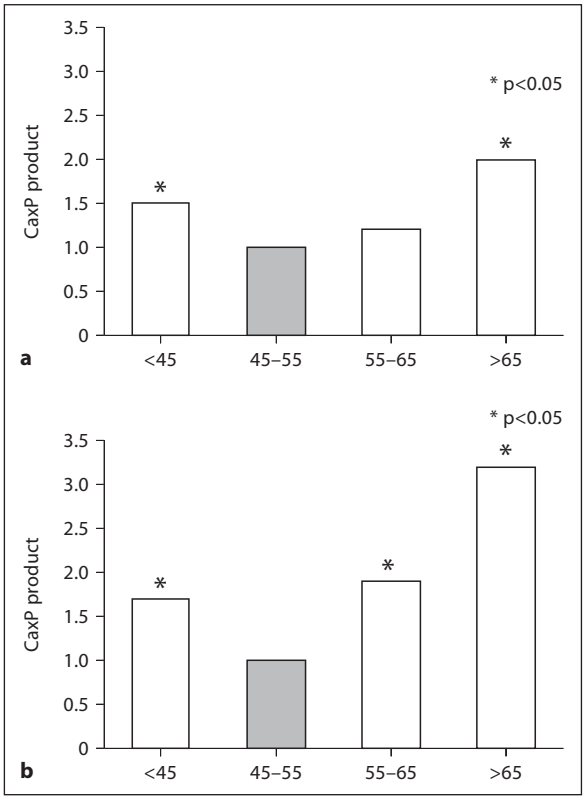

Fig. 4. Overall (**a**) and CV (**b**) mortality relative risk according to Ca x P product.

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Dr. Vincenzo Panichi
Nephrology and Dialysis, Versilia Hospital
Via Aurelia, 335, Lido di Camaiore
IT–55041 Camaiore Lucca (Italy)
Tel. + 39 0584 605 7238, E-Mail vpanichi@usl12.toscana.it

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