Chapter 6

Cardiovascular Risk Factors in End-Stage Renal Disease Patients: The Impact of Conventional Dialysis versus Online-Hemodiafiltration

Susana Coimbra, Maria do Sameiro Faria,
Vasco Miranda, Luís Belo and Alice Santos-Silva

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Abstract

End-stage renal disease (ESRD) patients present high incidence of cardiovascular (CV) events, which are the most common causes of death in these patients. The occurrence of CV events appears as a consequence of the high prevalence of traditional and non-traditional CV risk factors. Online-hemodiafiltration (OL-HDF) was introduced as a better alternative to conventional dialysis, as it was proposed to be more biocompatible, to increase dialysis efficacy, to reduce the inflammatory response to treatment and to improve patient's quality of life, contributing to reduce CV and all-cause mortality risk in ESRD. However, data in literature, comparing the effect of OL-HDF with conventional dialysis for clinical CV outcome and all-cause mortality, yielded controversy about those benefits of OL-HFD over standard hemodialysis. A review of the traditional CV risk factors (e.g., arterial hypertension, diabetes mellitus, dyslipidemia, obesity, smoking and advanced age), non-traditional risk factors (e.g., anemia, oxidative stress, hyperphosphatemia, endothelial dysfunction, left ventricular hypertrophy, insulin resistance, high levels of lipoprotein(a) and inflammation) and potential renocardiovascular biomarkers, in the setting of ESRD, is presented. The impact of conventional hemodialysis and OL-HDF on CV risk factors and on the outcome of ESRD patients is also addressed.

Keywords: cardiovascular risk factors, hemodialysis, online-hemodiafiltration, end-stage renal disease, inflammation, anemia

1. Introduction

Chronic kidney disease (CKD) prevalence is increasing worldwide and became an actual health challenge. CKD is a term used to refer heterogeneous disorders affecting kidney structure and function with variable clinical presentation which result in gradual to permanent loss of kidney function over time. Patients at higher risk for CKD include those with metabolic disorders, such as diabetes mellitus, obesity and amyloidosis, with arterial hypertension, renal vascular disorders, immunologic disorders, infections, primary tubular disorders (nephrotoxins), urinary tract obstruction (hypertrophy of prostate or renal calculi) and congenital disorders [1].

The two most common causes of CKD are diabetes and arterial hypertension; glomerulonephritis, nephrolithiasis and polycystic kidney disease are other, less common causes [2].

The patients at early stages of CKD (stages 1 and 2) are, usually, asymptomatic, showing kidney damage and/or loss of kidney function, with a significant risk for disease progression. At stages 3 and 4, worsening of the disease is associated with kidney dysfunction that progresses from mildly to severely decreased; in end-stage renal disease (ESRD), stage 5, an irreversible loss of renal function occurs. These patients require renal replacement therapy, such as dialysis or kidney transplantation.

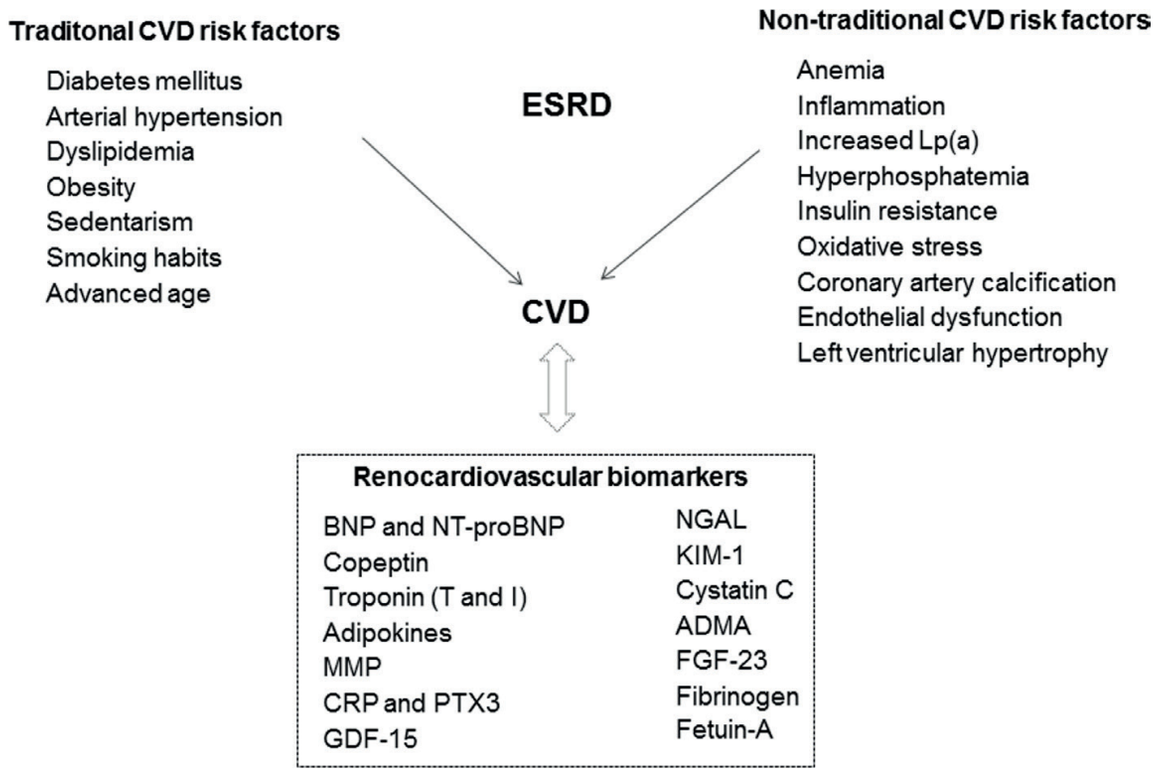

Figure 1. Traditional, non-traditional and potential renocardiovascular biomarkers in end-stage renal disease (ESRD). The high incidence of cardiovascular (CV) risk factors in ESRD contributes to the close relationship between CV disease (CVD) and ESRD (ADMA, asymmetric dimethylarginine; BNP, B-type natriuretic peptide; CRP, C-reactive protein; FGF-23, fibroblast growth factor-23; GDF-15, growth differentiation factor-15; KIM-1, kidney injury molecule-1; Lp(a), lipoprotein(a); MMP, matrix-metalloproteases; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, BNP amino-terminal fragment; PTX3, pentraxin 3).

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ESRD is a growing public health problem, given the increasing prevalence worldwide and its socioeconomic consequences. By 2020, it is estimated that the number of ESRD patients rises by 60%, as compared to the number of patients recorded in 2005 [3]. Mortality rate is 10- to 20-fold higher in ESRD patients than in general population [4]. These patients commonly present chronic inflammation, malnutrition and progressive cardiovascular disease (CVD) that is the most common cause of mortality (about 50%) [5]. These features have a considerable impact on functional status and health-related quality of life (HRQoL) of ESRD patients.

Dialysis therapies by using semipermeable membranes mimic renal function, removing the excess of water and waste products. Efficient cleansing of the blood from relevant uremic toxins, fluid and salt overload, is the prior goal of all dialysis therapies. Currently, different dialysis modalities, including peritoneal dialysis, hemodialysis and hemodiafiltration, are used for chronic and acute treatment of renal failure.

ESRD leads to impairment of HRQoL of the patients and to a higher risk of morbidity and mortality. Patients with ESRD present a higher incidence of CV events, as a result of the increased prevalence of CV risk factors, either traditional or non-traditional (**Figure 1**).

2. Cardiovascular risk factors

In the last two decades, the better understanding of uremic toxicity, salt and water control contributed to improve the CKD-associated comorbidities. Moreover, the recent advances in dialysis techniques have provided more efficient, controlled and safer dialysis procedures. In spite of these improvements, hemodialysis (HD) patients still present poor outcomes, with low survival rates, as compared to general population [6]. Morbidity and mortality in HD patients remains high in Europe and is higher in the United States [7]. CVD is the most common cause of death in CKD patients.

Based on the World Health Organization mortality database, Yoshino et al. [8] reported a close correlation between all-cause mortality rates and atherosclerotic CV disease mortality in the general population and that this correlation was even stronger for dialysis patients. United States Renal Data System (USRDS) 2013 Annual Data Report indicated that CKD patients have higher rates of congestive heart failure (CHF), acute myocardial infarction (AMI), cerebrovascular accidents and lower survival rates, as compared to non-CKD patients. Survival appears to decrease with severity of CKD [9]. Heart failure has been strongly related to CKD [10], suggesting a significant impact of the disease on cardiac structure and function.

The high incidence of CVD in CKD patients may result from the high prevalence of traditional CV risk factors and from other CKD-specific risk factors. In ESRD patients, worsening of the disease and the hemodialysis procedure may underlie the increased CV risk observed in these patients.

2.1. Traditional cardiovascular risk factors

Traditional CVD risk factors include diabetes mellitus, arterial hypertension, dyslipidemia, obesity, sedentarism, smoking habits, as well as advanced age.

2.1.1. Diabetes and hypertension

The MADIABETES Cohort Study showed that the coexistence of CKD in patients with type 2 diabetes mellitus was an independent risk factor for all-cause and CV mortality [11].

Arterial hypertension and diabetes, the main causes of CKD, lead to low glomerular filtration rate (GFR) and high albuminuria, inducing left ventricular hypertrophy and, subsequently, diastolic dysfunction of left ventricle [12]. It is known that albuminuria/proteinuria excretion is a marker of kidney damage and a risk factor for progression of kidney disease. More recently, it has been proposed to have a direct impact on CVD events in CKD patients. A prospective, population-based cohort study including 16,958 patients conducted in Iceland, showed that CKD patients at stage 3b or stage 4 had the highest risk for coronary heart disease (CHD); however, there was also a significant 1.55-fold increase in the risk of CHD in those patients with a GFR of at least 90 mL/min/1.73 m^2 with proteinuria (stage 1 CKD), and a significant 1.72-fold increase in risk of CHD in those with a GFR of 60–89 mL/min/1.73 m^2 with proteinuria (stage 2 CKD), as compared to the reference group without proteinuria [13]. According to Matsushita et al. [14], albuminuria is independently associated with heart mass, systolic and diastolic functions of left ventricle. The level of albumin is currently considered as a potential predictor of mortality and hospitalization risk [15].

Hypertension is found in 80–85% of CKD patients, and its etiology is multifactorial. The CKD per se favors the development of hypertension by activating renin-angiotensin and sympathetic nerve systems [16]. The activity of the sympathetic nervous system is enhanced in CKD patients, as a result of overspill and reduced catecholamine clearance, increasing vascular resistance and systemic blood pressure [17].

2.1.2. Dyslipidemia

CKD has been associated with an abnormal lipid profile, due to alterations in lipid metabolism; the most common changes in lipid profile include an increase in triglycerides (TG), lipoprotein (Lp)(a) and oxidized lipids, and a reduction in high-density lipoprotein cholesterol (HDLc) values. The hypertriglyceridemia may be explained by the increase in apolipoprotein C-III and by the reduction of lipoprotein lipase activity, reducing their clearance [18]. The decreased production of apolipoprotein A-1 with worsening of renal failure and the reduced activity of lecithin-cholesterol acyltransferase contribute to the reduction in HDL production [19]. Raised values of TG/HDLc ratio seem to be a predictor of poor CVD outcome in CKD patients [20].

In ESRD patients, the oxidative stress and the reduction in paraoxonase and glutathione peroxidase activities may compromise the antioxidant and anti-inflammatory properties of HDL that becomes dysfunctional [19]. These changes also explain the increase in oxidized low-density lipoproteins (oxLDL) and in oxLDL/LDLc ratio in CKD patients on dialysis [21]. The oxidative modifications in LDL are important for the initiation and progression of atherosclerosis and are well-known CVD risk factors.

2.1.3. Obesity

Obesity is a well-known CV risk factor that favors several comorbidities, such as type 2 diabetes, hypertension, dyslipidemia, cancer and sleep apnea. A meta-analysis that included 25 cohorts, 3 cross-sectional and 19 case-control studies reported that obesity also increases the risk for kidney disease in the general population [22]. There are several mechanisms through which obesity predisposes to CKD. High body fat mass favors mesangial expansion, increases renal metabolic demand, promoting glomerular hyperfiltration and hypertrophy, reduced podocyte density and increased filtration fraction, contributing to kidney damage and progression to ESRD [23]. The pattern of risk associated with obesity is different for ESRD on dialysis therapy, as these patients present a lower CV morbidity and mortality, known as "obesity paradox;" actually, morbidly obese HD patients present the lowest mortality rate [24]. Apparently, increased muscle and body fat mass promote longevity in advanced CKD.

Considering the continuous worldwide increase in obesity, it must be considered as an emerging problem for nephrologists and endocrinologists, deserving a especial care.

2.1.4. Smoking

Smoking habits, as obesity, is a major modifiable CV risk factor. Smokers, CKD patients without established CVD, have been associated with 59% increase in heart failure and 68% increase in peripheral vascular disease, as compared to non-smokers, in a follow-up study of 2.2 years [25].

The intervention of clinicians, in case of obesity and/or smoking habits, would contribute to minimize renal damage and progression of the disease; moreover, given the prevalence of CVD events, it would reduce morbidity and mortality in CKD patients.

2.2. Non-traditional cardiovascular risk factors

The non-traditional CV risk factors in CKD patients include the associated complications of the disease that usually grow worse in patients on dialysis therapy.

2.2.1. Anemia and inflammation

Anemia and inflammation are common features in CKD that increase as kidney function declines. Anemia is mainly due to the reduced production of erythropoietin (EPO) by the failing kidneys, leading to hypoxia that favors a local renal inflammatory process. In patients on HD, inflammation is enhanced, particularly in those using central venous catheter (CVC) for the vascular access in HD procedure. This type of vascular access is more prone to infection or inflammation, and thus, it might be associated with poor outcome of HD patients. Markers of inflammation, such as C-reactive protein (CRP) [26] and inflammatory cytokines [27], are raised in CKD patients, particularly in HD patients. In a recent study by our team, we found that CRP, malnutrition and the use of CVC were independent risk factors for mortality in HD patients [28].

Some uremic toxins express potent pro-inflammatory and oxidative activity [29], contributing to amplify inflammation and oxidative injuries to cells and plasma constituents. Dialysis therapy may directly benefit bone marrow erythropoiesis, by removing substances that inhibit erythropoiesis. Nowadays, HD membranes are highly biocompatible; however, long-term intradialytic contact of blood with large surfaced artificial materials leads to continuous inflammatory cell activation, with release of cytokines and reactive oxygen species (ROS) and nitric oxide production.

Apparently, inflammation and oxidative stress play crucial roles in the progression of CKD and in the risk for CVD events [30]. Inflammation is also associated with endothelial dysfunction, which is observed even in the initial phases of CKD [31]. Moreover, inflammation seems to be independently associated with anemia and malnutrition, leading to accelerated atherosclerosis, CV complications or even death [32]. Actually, it was recently recommended to monitor inflammation through the evaluation of inflammatory markers in CKD patients, since persistent inflammation may be a silent reflection of pathophysiologic disturbances [33]. CRP seems to be the most useful biomarker in clinical practice for guidance of inflammation and to estimate risk in CKD patients [33].

Anemia can lead to adverse clinical effects, namely reduction in tissue oxygenation, increase in cardiac output, left ventricular hypertrophy, congestive heart disease, fatigue, reduction in exercise capacity, and immunodeficiency. Besides the insufficient renal production of EPO, other factors may contribute to enhance anemia. Uremic toxins are able to suppress erythropoiesis, by inhibiting proliferation of erythroid progenitors [34]. The activation of inflammatory cells is accompanied by the release of inflammatory cytokines, as interleukin (IL)-6 that triggers the synthesis of hepcidin, by the liver. This glycoprotein, increased in CKD patients, is the main regulator of iron metabolism. Hepcidin reduces iron absorption through enterocytes and the mobilization of iron from macrophages of the reticuloendothelial system, leading to a functional iron deficiency that will further worsen anemia. Increasing hepcidin levels, decreasing EPO levels and increasing impairment of kidney function were reported as independent predictors of mortality in CKD diabetic patients [35].

Chronic blood loss, due to bleeding events, accidental losses, excessive blood drawn for laboratory tests, and blood lost within dialysis circuit after HD sessions, may also contribute to the anemic state [34].

It is also important to refer that erythrocytes of patients with CKD are more prone for premature removal, showing a shorter life span. Changes in erythrocyte membrane protein composition, namely in spectrin and band 3, have been reported in HD patients. Alterations in membrane protein interactions may lead to destabilization of membrane structure, favoring a premature removal of the erythrocytes [36].

2.2.2. Oxidative stress

An enhanced production of ROS and a decrease in antioxidants favor oxidative stress, a common condition in ESRD. This imbalance of oxidants/antioxidants favors tissue damage, through lipid, protein, and DNA oxidation, that may lead to endothelial dysfunction and atherosclerosis [37]. As referred previously, increased levels of oxLDL, a key player in

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the initiation and progression of atherosclerosis, and a higher oxLDL/LDLc ratio have been reported in CKD patients on dialysis [21]. Products of lipid peroxidation, such as malondialdehyde and hydroperoxide, are increased in CKD, being the latter reported as a reliable marker of oxidative injury during HD [38]. Advanced oxidation protein products accumulate in CKD, especially in HD patients, and have been reported as independent risk factors for ischemic heart disease [39]. Moreover, HD seems to contribute to oxidative stress being associated with increased synthesis of pro-inflammatory cytokines, phagocyte oxidative burst, activation of NADPH oxidase, and antioxidant removal by dialysis [40].

2.2.3. Other factors

Several other uremic-related factors may also play an important role in CVD risk of these patients, namely multiple comorbid conditions, fluid overload, hyperphosphatemia, endothelial dysfunction, left ventricular hypertrophy, insulin resistance (IR), hyper-homocysteinemia and high levels of Lp(a).

Lipoprotein(a), known as an independent risk factor for CVD, is increased in HD patients [21], but the mechanism explaining this rise is still poorly understood. It has been suggested that it results, mainly, from a decrease in Lp(a) clearance, than from an increased production [41].

The atherothrombogenicity of Lp(a) is associated with a structural homology of apo(a) and plasminogen that seems to lead to a competition for the linkage to fibrin, inhibiting fibrinolysis. Lp(a) as LDL is crucial for the initiation, progression and rupture of the atherosclerotic plaque; the oxidation of apo(a) triggers the binding to scavenger receptors on macrophages and the avid uptake of Lp(a).

Mild-to-moderate CKD patients, and even those with a GFR within normal values, often develop IR. In ESRD patients, IR has been linked to protein energy wasting and malnutrition and appears as an independent predictor for CVD [42].

Hyperphosphatemia is a marker of kidney function decline and has been reported as a marker of increased risk for CVD events and mortality [43].

Coronary artery calcification has a significant incidence in patients with CKD. Recently, Chen et al. [44] reported that in CKD patients, coronary artery calcification is independently and strongly associated with risk for CVD, myocardial infarction, heart failure and all-cause mortality. The authors suggested the inclusion of coronary artery calcification as a criteria for risk stratification and prediction of CVD among CKD patients [44].

A recent study by Chen et al. [45] in CKD patients showed that inflammation, prothrombotic state, oxidative stress, IR, enhanced glycated hemoglobin and increased alkaline phosphatase are associated with an increased risk for peripheral arterial disease, independent of traditional risk factors.

2.3. Renocardiovascular markers

Cardiorenal syndrome traduces the close relationship between CVD and CKD [46]; in these conditions, the dysfunction in one organ often induces a dysfunction in the other.

Given the high prevalence of CVD in CKD patients, particularly in those on hemodialysis, some biomarkers, pertinent for both conditions, have emerged and were defined as renocardiovascular biomarkers [47]. Several hormones, biomarkers of cardiac injury, oxidative stress, renal damage and inflammation have been proposed for the group of potential biomarkers of cardiorenal syndrome [47] (**Figure 1**).

Natriuretic peptides and related peptides, endothelin, argine vasopressin, copeptin and adrenomedullin are some of the neurohormones under study as cardiorenal syndrome biomarkers.

2.3.1. B-type natriuretic peptide

B-type natriuretic peptide (BNP) and its amino-terminal fragment (NT-proBNP), produced when hemodynamic load occurs, seem to be the best markers for heart failure and are also used for other CVD [47, 48]. Both BNP and NT-proBNP seem to be also valuable biomarkers for progression of CKD, prediction of mortality and stratification of CV risk in patients in dialysis [49, 50].

2.3.2. Copeptin

Copeptin, the C-terminal part of pro-arginine vasopressin is known as a substitute marker of arginine vasopressin; it has been associated with CV and all-cause mortality in type 2 diabetes mellitus patients treated in primary care [51]. Fenske et al. [52] reported that copeptin showed significant associations with stroke, sudden death, combined CV events and mortality, in type 2 diabetes mellitus patients on hemodialysis, but not with myocardial infarction or death caused by CHF. However, the value of copeptin and arginine vasopressin as biomarkers of CVD in CKD may be limited, as the impairment in renal function seems to introduce a bias, by altering the clearance of the two peptides [53].

2.3.3. Troponin

Some markers of cardiac injury have been also proposed as cardiorenal biomarkers, such as troponin. It is known that when acute myocardial injury occurs, myocytes release cardiac troponin (T and I) within 3–12 h; a mean peak in its circulating values is achieved after 12–48 h, returning to baseline levels in 5–14 days. Asymptomatic subjects with increased troponins have a threefold risk in all-cause and CV mortality [54]. A recent meta-analysis reported a close association between increased levels of cardiac troponins and increased risk of coronary artery disease in CKD patients [55]. According to National Academy of Clinical Biochemistry Laboratory Medicine Practice guidelines, a change of ≥20% in cardiac troponins, in ESRD patients, is a good marker for acute coronary syndrome [56].

Reinforcing the link between cardiac damage and ESRD development, it was reported that the levels of cardiac troponin T and NT-proBNP are independent predictors of ESRD risk in the general population, as well as, in subjects with diabetes mellitus and anemia [57].

2.3.4. Adiponectin and leptin

In both CKD and CVD patients, an abnormal lipid profile is common, as well as an altered production of adipokines. Adiponectin and leptin have been also proposed as cardiorenal

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biomarkers. High levels of adiponectin and leptin are common in CKD patients; however, this change in adiponectin has been associated with increased risk of mortality; hyperleptinemia has been associated with several CVD risk factors, such as inflammation, IR, protein energy wasting, and with progression of CKD, by favoring hypertension and fibrosis [58].

2.3.5. Matrix-metalloproteases

Renal fibrosis seems to progress through several steps: inflammation, activation and transformation of fibroblast to myofibroblast, matrix deposition and fibrosis. Matrix-metalloproteases (MMP) have an important role in fibrosis and are also vital in angiogenesis and vascular remodeling; their activation may alter the architecture of the atherosclerotic plaque, participating in plaque rupture processes. In CKD, MMP-2 showed a positive and reliable association with carotid intima-media thickness [59]. However, further studies are needed to investigate the association of MMPs and other matrix-related markers, such as galectin-3 and ST2, with CVD in CKD patients. Galectin-3, secreted by macrophages and known for its role in mediating cardiac fibrosis and inflammation, was approved by the US Food and Drug Administration as a new biomarker for HF risk [60].

2.3.6. CRP and PTX3

A persistent mild-to-moderate inflammation is common in CKD patients and enhanced in ESRD patients. Inflammation is able to amplify other common features, as oxidative stress, atherosclerosis, vascular calcification, depression and protein energy wasting, acting as a catalyst of risk factors for ESRD. Several studies showed the association between biomarkers of systemic inflammation, as CRP, IL-6, tumor necrosis factor-alpha and fibrinogen, with lower kidney function [61]. Moreover, several pro-inflammatory cytokines have been associated with a higher risk for CV events and for mortality.

According to Dialysis Outcomes and Practice Patterns Study (DOPPS), III study, CRP measurement is increasing in most countries [62]. This study showed that CRP monitoring within a dialysis facility is significantly associated with a lower CV mortality, suggesting that this practice may benefit patient's outcome. Indeed, an increase in CRP, showing worsening of inflammation, would trigger the search for underlying causes, allowing a more rapid clinical intervention and a better outcome. This study also showed that the relation of CRP to mortality was independent of other common inflammatory markers.

Pentraxin 3 (PTX3), produced by resident and innate immunity cells in peripheral tissues, increases rapidly within the primary local of activation, triggering the inflammatory response. Thus, while CRP is produced by hepatocytes, PTX3 is synthesized at the site of inflammation. It increases as renal function declines and predicts CV and overall mortality risk in CKD patients. PTX3 also plays regulatory functions in angiogenesis, atherosclerosis, apoptotic cell clearance and tissue repair [63]. The rapid increase in PTX3 expression in vascular endothelial cells, following an inflammatory stimulus, showed that it could be a useful marker for vascular pathology. Indeed, PTX3 seems to be a powerful marker of inflammation and a good biomarker for development and progression of atherosclerosis.

2.3.7. Growth differentiation factor 15

Growth differentiation factor 15 (GDF-15) has been also associated with inflammation, as well as with cancer, aging, diabetes mellitus and atherosclerosis, emerging as strong risk factor for mortality in individuals with existing CVD. High GDF-15 levels also reflect progressive kidney dysfunction and poor outcome in CKD patients [64].

2.3.8. Neutrophil gelatinase-associated lipocalin

The activation of inflammatory cells is accompanied by the release of several pro-inflammatory cytokines that have been associated with a higher risk for CV events and for mortality, in CKD patients. Neutrophil activation is accompanied by metabolic burst with production of oxygen metabolites and release of granule content, contributing to oxidative stress and to the inflammatory response. Neutrophil gelatinase-associated lipocalin (NGAL) is a marker of neutrophil activation that appears as an early biomarker of acute kidney injury. This glycoprotein has been also related to atherosclerosis and CVD [47]. Urinary NGAL levels seem to be independently associated with ischemic atherosclerotic events [65]. Furuya et al. [66] reported that NGAL levels were higher in HD patients with CVD, when compared to patients without CVD.

2.3.9. Kidney injury molecule-1

Kidney injury molecule-1 (KIM-1) is another biomarker of kidney injury. After proximal tubular injury, the transmembrane protein KIM-1 is highly upregulated. Sabbisetti et al. reported that KIM-1 levels are elevated in CKD patients, and in patients with type 1 diabetes mellitus and proteinuria, the circulating levels of KIM-1 predict the loss of estimated GFR (eGFR) and the risk for ESRD [67]. The Chronic Renal Insufficiency Cohort (CRIC) study reported that CKD patients in the highest two quintiles of KIM-1/creatinine (Cr) values had a higher risk of heart failure, as compared to those in the lowest quintile. Moreover, the ratio KIM-1/Cr was independently associated with atherosclerotic CVD events, and the ratios KIM-1/Cr and NGAL/Cr were associated with all-cause death [68].

2.3.10. Other markers

Other early biomarkers of renal dysfunction, as liver-type fatty acid binding protein and cystatin C, might be useful in the early detection of renal involvement in CVD patients. Increased levels of cystatin-C in CKD patients have been associated with CVD risk, as well as with all-cause mortality [69].

Considering that both CKD and CVD have oxidative stress as a common feature, some oxidative stress biomarkers, as malondialdehyde, oxLDL, advanced glycation end-products, have been proposed as potential renocardiovascular markers of risk.

Uric acid has also emerged as a risk factor for progression of CKD that might be also linked to CVD risk; however, it is not clear whether hyperuricemia plays a causative role in CKD progression or is only a biomarker of kidney dysfunction [70].

Asymmetric dimethylarginine (ADMA), an amino acid found in tissues and cells, acts as an endogenous inhibitor of nitric oxide synthase and has emerged as a biomarker of endothelial dysfunction, CVD risk, and CKD outcome [71].

The disturbances in mineral metabolism observed in CKD patients play a crucial role in the development of CVD, and some biomarkers have been proposed as potential renocardiovascular biomarkers, such as fibroblast growth factor (FGF)-23, fetuin A, osteoprotegerin, vitamin D and parathyroid hormone. FGF-23 seems to be a promisor CVD biomarker both in subjects without renal dysfunction and in CKD and ESRD patients, especially in the last ones [47]. In a prospective cohort of 3860 patients with CKD stages 2–4, enhanced FGF-23 levels were associated with higher risk of CVD, especially with CHF [72]. FGF-23 seems to regulate the production of fetuin-A, a glycoprotein with anti-calcification activity [73]. Considering the crosstalk between these two proteins, both appear as promising renocardiovascular biomarkers.

Progressive loss of kidney function is linked to a reduction in the production of vitamin D and to a disturbance in serum calcium and phosphorus balance that have been associated with poor CKD outcome and to increased risk for CVD events and mortality [74].

Fibrinogen, a glycoprotein involved in blood clot formation, is a marker of CVD in the general population and was also pointed as a marker of CV and all-cause mortality in ESRD patients [69].

The relationship between CV events and CKD/ESRD is complex and poorly understood. A better understanding of this relationship might be helpful for the validation of these potential renocardiovascular biomarkers and, eventually, for the identification of new biomarkers. The definition of a biomarker or a panel of biomarkers to evaluate CVD risk in CKD patients will be a great achievement. Meanwhile, further studies are needed to confirm if the biomarkers that have emerged are good and reliable biomarkers of CV risk in CKD.

3. Hemodialysis versus online-hemodiafiltration

Advanced age and comorbid conditions at starting dialysis, as well as efficacy and quality of renal replacement therapy, are some of the factors that affect dialysis patient's mortality. Dialysis techniques, applied for more than 50 years, have clearly improved over the last few years; however, despite refinements of dialysis therapy, both CV and all-cause mortality rates in ESRD patients treated with conventional HD remain significant.

The introduction of online-hemodiafiltration (OL-HDF), by combining HD and hemofiltration (HF) modalities, was believed to improve patient's outcome, namely their QoL, morbidity and mortality. HDF combines diffusive and convective transport through a high-flux dialysis membrane. The convective transport is achieved by filtering a volume of plasma water substantially in excess of that needed to achieve dry weight and, at the same time, by infusing a sterile substitution fluid directly into the patient's bloodstream. The substitution fluid is prepared online and can be administered before (predilution) or after (postdilution) the dialyzer.

It has been proposed that OL-HDF increases the dialysis efficacy, by removing uremic toxins with higher molecular weight up to middle and large solutes; ameliorates the clinical tolerance

to HD sessions; improves patient's HRQoL; and improves the biocompatibility of the dialysis system, through the combination of the use of high flux synthetic membranes with ultrapure dialysis fluid purity [75, 76].

Some studies comparing cost-effectiveness of OL-HDF and HD reported that HD is more cost-effective; however, a recent analysis by Ramponi et al. [77] showed that OL-HDF is as cost-effective as high-flux HD. An advantage over high-flux HD is the substantial effect of OL-HDF on the improvement of patient's satisfaction and QoL [78]. Another advantage of OL-HDF over HD procedure is its higher biocompatibility and dialysis efficacy that appears to improve the outcome of ESRD patients. Indeed, by reducing the inflammatory response and the associated complications, it would, probably, contribute to reduce the high morbidity and mortality of ESRD patients [75, 76, 79, 80]. For instance, OL-HDF showed more favorable acute and short-term effects than conventional HD on markers of endothelial dysfunction, namely on flow-mediated dilatation of the brachial artery, soluble endothelial protein C receptor and soluble thrombomodulin [81].

A summary of some studies comparing long- or medium-term effects of OL-HDF and HD is presented in **Table 1**.

A study performed in 2006 that enrolled 2165 patients, stratified into low- and high-flux HD and low- and high-efficiency HDF groups, reported that high-efficiency HDF patients presented a significant 35% lower mortality risk than those receiving low-flux HD; the authors also reported that HDF may improve patient's survival independently of (a higher) dialysis dose [82].

The prospective and observational RISCAVID study also reported a better survival with OL-HDF therapy versus HD [83]. A retrospective study reported that ESRD patients predominantly treated with OL-HDF showed also a better survival, as compared to patients treated with high-flux HD therapy; nonetheless, according to the authors mortality benefit with HDF needs confirmation; no benefits were detected for anemia management, nutrition, mineral metabolism and blood pressure control [84].

In the Grooteman study [85], the CONvective TRAnsport STudy (CONTRAST), 714 chronic HD patients were evaluated, 358 on OL-HDF and 356 on low-flux HD. After a 3-year follow-up study (range 0.4–6.6 years), no significant beneficial differences in all-cause mortality and CV events were found between the two groups. Further analysis suggested a possible benefit for survival of patients under high-volume HD treatment in the group of patients with the highest delivered convection volume (upper tertile >21.95 L); mortality in these patients was considerably lower than in those randomized to low-flux hemodialysis.

In a multicenter, open-label, randomized controlled trial [86], the ESHOL or Catalonian hemodiafiltration study, 906 chronic HD patients were enrolled in the study; 456 switched to high-efficiency postdilution OL-HDF and 405 continued on HD; a reduction in all-cause mortality was observed for OL-HDF, when compared to conventional HD treatment. Patients assigned to OL-HDF, as compared to HD, had a 30% lower risk of all-cause mortality, a 33% lower risk of CV mortality, and a 55% lower risk of infection-related mortality. Moreover, the dialysis sessions complicated by hypotension and all-cause hospitalization presented lower incidence rates in patients receiving OL-HDF. A reanalysis of the ESHOL study showed that in prevalent patients, postdilution OL-HDF, versus HD, reduced all-cause mortality [87].

Authors	Year	Study length	Patients	Major findings
Canaud et al. [82]	2006	3 y	n = 2165	HDF may improve patient survival independently of (a higher) dialysis dose
Panichi et al. [83]	2008	30 m	n = 757	HDF was associated with an improved cumulative survival, independently of dialysis dose
Vilar et al. [84]	2009	Retrospective study (18-y period)	n = 858	No benefits of HDF over high-flux HD for anemia management, nutrition, mineral metabolism and BP control; mortality benefit with HDF needs confirmation
Grooteman et al. [85]	2012	3 y (mean)	n = 714 (358: OL-HDF; 356: HD)	No beneficial effect of HDF on all-cause mortality and CV events compared with low-flux HD; possible survival benefit for HDF (requires confirmation)
Maduell et al. [86]	2013	1.91 ± 1.10 y	n = 906 (456: OL-HDF; 450: HD)	High-efficiency OL-HDF reduces all-cause mortality, compared with conventional HD
Ok et al. [88]	2013	22.7 ± 10.9 m	n = 782	All-cause mortality and nonfatal CV event rate were similar for OL-HDF and high-flux HD groups; in a post hoc analysis, OL-HDF treatment with substitution volumes over 17.4 L was associated with better CV and overall survival
van der Weerd et al. [89]	2014	12 m	n = 714	Compared to low-flux HD, OL-HDF treatment did not decrease ESA resistance
Mostovaya et al. [90]	2014	4 y	n = 342	OL-HDF did not affect changes in LVM, VEF or PWV over time, compared with HD
Siriopol et al. [91]	2015	Retrospective study (3 y)	n = 1546 (1322: HD; 224: HDF); n = 2447 (2181: HD; 266: HDF)	HDF reduced all-cause mortality in incident and prevalent patients, even after correction for different confounders
Mercadal et al. [92]	2016	1.95 y (median)	n = 28,407 (5526 used HDF for a median of 1.2 years; 2254 of them used HDF exclusively)	HDF treatment was associated with better survival
Smith et al. [93]	2016	8 w of HD followed by 8 w of OL-HDF (or vice versa)	n = 100	Similar posttreatment recovery time and HRQoL scores

BP, blood pressure; CV, cardiovascular; ESA, erythropoiesis-stimulating agents; HRQoL, health-related quality of life; LVM, left ventricular mass; OL, online; PWV, pulse-wave velocity; VEF, ventricular ejection fraction; w, week; m, months; y, year.

Table 1. Some of hemodialysis (HD) versus hemodiafiltration (HDF) studies.

The Turkish OL-HDF Study [88], a follow-up study of nearly 2 years, found that the prevalence of death from any cause and of nonfatal CV events was similar for OL-HDF and for high-flux HD groups; CV and overall survival, hospitalization rate and number of hypotensive episodes were also similar; however, a subgroup of OL-HDF patients treated with substitution volumes over 17.4 L, above the median convective volume, presented a better CV and overall survival, when compared to HD patients. It was also reported that small solute clearance was higher in OL-HDF group and, in spite of the similar hemoglobin levels in the two groups, the prescribed dose of EPO and the erythropoietin resistance index were significantly lower in OL-HDF group. The increase in EPO response seems to be due to the higher clearance of middle-sized molecules and to the improvement in the microbiological quality of fluids used in OL-HDF procedures that may contribute to reduce systemic inflammation. In opposition, the trial CONTRAST [89], a 12-month follow-up study of 714 patients randomized to either treatment with online postdilution HDF or continuation of low-flux HD showed that OL-HDF treatment did not decrease the index of resistance to erythropoiesis-stimulating agents, when compared to HD treatment.

Cardiovascular parameters, as left ventricular mass, ventricular ejection fraction and pulse-wave velocity, are altered in ESRD patients and are usually associated with CV mortality. A study by Mostovaya et al. [90] showed that OL-HDF did not improve these CV parameters over time, when compared to HD therapy.

A retrospective analysis by Siriopol et al. [91] on Romanian dialyzed population, using the European Clinical Database (EUCLID) Fresenius Medical Care Database, showed that HDF reduced all-cause mortality in incident and prevalent patients, even after correction for different confounders; however, other unmeasured confounders could have influenced their final results [91].

Analysis of data from the French National Renal Epidemiology and Information Network (REIN) registry, enrolling 28,407 patients (5526 switched for HDF; 2254 were only treated with HDF and the others were treated with HD), reported that patients exclusively on HDF presented the best survival [92].

In a recent randomized, single-blind, crossover trial, HD and HDF patients showed similar posttreatment recovery time and HRQoL [93].

A systematic review conducted in 2006, analyzed 20 trials including 657 patients, reported inconclusive data concerning the improvement of convective therapies (HDF, hemofiltration and acetate-free biofiltration), versus HD, on mortality, dialysis-related hypotension and hospitalization [94].

A 2014 meta-analysis of 16 randomized trials [95] (three large trials were already referred [85, 86, 88]), including 3220 ESRD patients, focused and compared the effect of convective modalities (hemofiltration and HDF), with standard dialysis. This meta-analysis demonstrated that HDF did not alter significantly clinical CV outcome rates. Indeed, the effect of convective modalities on clinical CV outcome was not statistically different, when compared to either low-flux or high-flux HD treatment. Moreover, convective modalities, as compared to standard dialysis, showed no different all-cause mortality rates; in addition, mortality rate was independent of the type of convective modality. It was also reported that systolic

blood pressure, at end of the treatments, was similar for convective modalities and standard HD. Dialysis adequacy was also similar, although there were evidences of heterogeneity within data from the different studies. The convective modalities seem to reduce significantly postdialysis serum levels of β_2-microglobulin. HRQoL was evaluated in three trials, and no significant differences in physical symptoms domain scores were observed between convective modalities and standard dialysis.

In opposition, another meta-analysis reported in 2014 [96], including six randomized controlled trials, comparing online postdilution HDF with HD treatment, showed a reduction in mortality risk and CV death for patients treated with online postdilution HDF; moreover, when considering the three largest randomized controlled trials, an inverse relation between convection volume magnitude and mortality risk was observed. The authors highlighted that the randomized controlled trials analyzed in this meta-analysis contained several potential risks of bias that may over- or underestimate the effects.

In 2015, another systematic review comparing convective modalities with HD therapy included a higher number of studies and ESRD patients (40 studies, 4137 patients) [97]. This meta-analysis showed that convective therapies may contribute to reduce CV mortality, but not all-cause mortality; the benefits on CVD events, hospitalization and QoL versus HD, were once again not conclusive [97].

Based on individual participant data of four large multicenter randomized controlled trials, it was recently reported (2017) that OL-HDF, compared to conventional HD, reduces the risk of mortality in ESRD patients [98]. Using the same individual participant data, Nubé et al. [99] conducted a study to investigate whether the reduction on mortality risk associated with HDF resulted from a reduction in CVD events and which type of CV events explained that reduction. A decrease in fatal ischemic heart disease and congestion appeared to underlie the positive effect of OL-HDF on CV and all-cause mortality.

The French Convective versus Hemodialysis in Elderly (FRENCHIE) study aimed to compare intradialytic tolerance of OL-HDF versus high-flux HD [100]. A significantly lower occurrence of adverse events, with fewer episodes of intradialytic symptomatic hypotension and muscle cramps, was found for OL-HDF patients; moreover, serum albumin values were similar, but an improvement in metabolic bone disease biomarkers and in β_2-microglobulin levels was found [100]. HRQoL, morbidity and mortality were similar for both treatments.

In summary, the improvement on all-cause mortality and on CVD events for OL-HDF treatment is still controversial, and therefore, it is not entirely clear if OL-HDF is, actually, a better alternative to standard HD.

4. Conclusions remarks

ESRD patients present high mortality and incidence of CV events. The occurrence of CVD events appear as a consequence of the high prevalence of traditional and non-traditional CV risk factors in these patients.

OL-HDF, an alternative to standard dialysis, was introduced as a better alternative to conventional dialysis. Nevertheless, convective modalities benefits versus standard dialysis, in what concern CV outcome or all-cause mortality remain questionable. Regarding clearance of small molecules, no evidence exists of a superior effect [95], though convective modalities appear to diminish the incidence of symptomatic hypotension and to enhance middle-molecular clearance (as assessed by β_2-microglobulin). One possibility is that the delivered dose of HDF was not sufficient, considering that in two of the larger trials [85, 88], a positive association between higher convective volume replacement and better relative outcomes was observed. Indeed, the importance of convective volume to improve survival of OL-HDF patients has been highlighted [101]. Higher convection volumes in OL-HDF were associated with higher patient's survival; however, results varied across different ways of standardization for body size, suggesting that further studies should consider body size [102]. Apparently, when adequate convection volumes are used, OL-HDF reduces all-cause and CV mortality risk.

Data from clinical trials and meta-analyses are controversial and not conclusive. It is not clear if OL-HDF is really a reliable alternative to HD in what concerns all-cause mortality and CVD events. We must consider that the studies about these issues are still too small or too short in duration, to detect a true benefit. Thus, further trials, with larger number of patients, involving longer follow-up periods and, eventually, with patients receiving higher volume replacement, to increase the precision of the survival analyses and to evaluate the real impact of OL-HDF procedure in mortality and CV outcome of ESRD patients are necessary.

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Author details

Susana Coimbra[1,2], Maria do Sameiro Faria[3,4], Vasco Miranda[3], Luís Belo[5] and Alice Santos-Silva[5]*

*Address all correspondence to: assilva@ff.up.pt

1 CESPU, Institute of Research and Advanced Training in Health Sciences and Technologies (IINFACTS), Gandra-PRD, Porto, Portugal

2 UCIBIO\REQUIMTE, Porto, Portugal

3 NephroCare Hemodialysis Clinic, Maia, Portugal

4 Unit of Pediatric Nephrology, Centro Materno Infantil do Norte, Porto, Portugal

5 UCIBIO\REQUIMTE, Department of Biological Sciences, Laboratory of Biochemistry, Faculty of Pharmacy, University of Porto, Porto, Portugal

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