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Bisphenol A and chlorinated derivatives of bisphenol A assessment in end stage renal disease patients: Impact of dialysis therapy

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ABSTRACT

Patients with end stage kidney disease treated by dialysis (ESKDD) process dialysis sessions to remove molecules usually excreted by kidneys. However, dialysis therapy could also contribute to endocrine disruptors (ED) burden. Indeed, materials like dialyzer filters, ultrapure dialysate and replacement fluid could exposed ESKDD patients to Bisphenol A (BPA) and chlorinated derivatives of BPA (ClxBPAs). Thus, our aim was to compare BPA and ClxBPAs exposure between ESKDD patients, patients with stage 5 chronic kidney disease (CKD5) not dialyzed and healthy volunteers. Then we describe the impact of a single dialysis session, according to dialysis modalities (hemodialysis therapy (HD) *versus* online hemodiafiltration therapy (HDF)) and materials used with pre-post BPA and ClxBPAs concentrations. The plasma levels of BPA and four ClxBPAs, were assessed for 64 ESKDD patients in pre and post dialysis samples (32 treated by HD and 32 treated by HDF) in 36 CKD5 patients and in 24 healthy volunteers. BPA plasma concentrations were 22.5 times higher for ESKDD patients in pre-dialysis samples *versus* healthy volunteers (2.208 ± 5.525 ng/mL *versus* 0.098 ± 0.169 ng/mL) ($p < 0.001$). BPA plasma concentrations were 16 times higher for CKD5 patients *versus* healthy volunteers, but it was not significant (1.606 ± 3.230 ng/mL *versus* 0.098 ± 0.169 ng/mL) ($p > 0.05$). BPA plasma concentrations for ESKDD patients in pre-dialysis samples were 1.4 times higher *versus* CKD5 patients (2.208 ± 5.525 ng/mL *versus* 1.606 ± 3.230 ng/mL) ($p < 0.001$). For healthy volunteers, ClxBPAs were never detected, or quantified while for CKD5 and ESKDD patients one ClxBPAs at least has been detected or quantified in 14 patients (38.8%) and 24 patients (37.5%), respectively. Dialysis therapy was inefficient to remove BPA either for HD (1.983 ± 6.042 ng/mL in pre-dialysis *versus* 3.675 ± 8.445 ng/mL in post-dialysis) or HDF (2.434 ± 5.042 ng/mL in pre-dialysis *versus* 7.462 ± 15.960 ng/mL in post dialysis) regarding pre-post BPA concentrations ($p > 0.05$). The same result was observed regarding ClxBPA analysis. Presence of polysulfone in dialyzer fibers overexposed ESKDD patients to BPA in pre-dialysis samples with 3.054 ± 6.770 for ESKDD patients treated with a polysulfone

List of abbreviations: BMI, Body mass index; BPA, Bisphenol A; BPF, Bisphenol F; ClxBPAs, Chlorinated derivatives of Bisphenol A; CKD5, Stage 5 Chronic Kidney Disease; DCBPA, 2,2'-dichlorobisphenol A and 2,6'-dichlorobisphenol A; EDCs, Endocrine Disrupting Chemicals; ESKDD, End stage kidney disease treated by dialysis; FBE, French Blood Establishment; HD, Hemodialysis therapy; HDF, Online hemodiafiltration therapy; IS, internal standard; LOD, Limit of detection; LOQ, Limit of quantification; MCBPA, Monochlorobisphenol A; QCs, Quality controls; SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks; SD, standard deviations; TCBPA, Trichlorobisphenol A; TTCBPA, Tetrachlorobisphenol A.

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dialyzer versus 0.708 ± 0.638 ($p = 0.040$) for ESKDD patients treated without a polysulfone dialyzer and to BPA in post-dialysis samples with 6.629 ± 13.932 for ESKDD patients treated with a polysulfone dialyzer versus 3.982 ± 11.004 ($p = 0.018$) for ESKDD patients treated without a polysulfone dialyzer. This work is to our knowledge the first to investigate, the impact of a dialysis session and materials used on BPA and ClxBPAs plasma concentrations and to compare these concentrations to those found in CKD5 patients and in healthy volunteers.

1. Introduction

In 2002, the World Health Organization defined Endocrine Disrupting Chemicals (EDCs) as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny” (World Health Organization, 2002). Bisphenol A (BPA), is the most well known ubiquitous pollutants exhibiting endocrine properties (Acconcia et al., 2015; ECHA, 2017). The World Health Organization has highlighted the massive use of BPA in the production of polycarbonate, polysulfone, epoxy resins and in many plastic consumer products (FAO/WHO Expert, 2010; Hipwell et al., 2019; Vandenberg et al., 2007). Therefore BPA has been found in the environment, including surface waters (Leusch et al., 2018) and tap water (Dupuis et al., 2012). In many countries, a chlorination step is often required to produce drinking water. However, BPA could react with chlorine disinfectants in addition of chlorine atoms to the phenolic rings leading to the production of chlorinated derivatives (ClxBPAs) (Gallard et al., 2004; Lane et al., 2015). These compounds have been characterized by an estrogenic activity up to 38 times higher than BPA itself (Fukazawa et al., 2002). BPA exposure has been related to reproductive disorders, cardiovascular diseases and metabolic disorders (Kahn et al., 2020; Rezg et al., 2014). ClxBPAs have been related to metabolic disorders such as diabetes and cardiovascular risks (Andra et al., 2015b; Hu et al., 2019; Plattard et al., 2021). Synergistic or antagonistic mechanisms have been described for these micropollutants when they are simultaneously present in environment. These cocktail effects are key points of EDCs toxicology (Le Magueresse-Battistoni et al., 2017).

Due to their ubiquitous properties humans are frequently exposed to various EDCs and several populations are particularly at risk due to the long-term exposure and the already malfunctioning of the kidney, a relevant target organ for BPA toxicity. In 2015, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded that risk for adverse effects with BPA may exist when BPA is directly available for systemic exposure, especially for patients with end stage kidney disease treated by dialysis (ESKDD) (Testai et al., 2016). However, health and safety conditions governing the practice of dialysis do not include risks related to the occurrence of EDCs such as BPA and ClxBPAs. Indeed, patients with reduced renal clearance were demonstrated to be highly exposed to BPA (Krieter et al., 2013). Regarding the removal of BPA during dialysis therapy, only a small amount of free BPA (5 to 26%, unbinding to protein) could pass through the hemodialysis membrane. Thus, BPA elimination is limited (Csanády et al., 2002; Krieter et al., 2013). Due to this property, online hemodiafiltration therapy (HDF) which combines diffusive and convective solute transport seems to better remove BPA than conventional hemodialysis therapy (HD) only based on diffusive transport (Mas et al., 2018; Quiroga et al., 2016). Furthermore, it has been demonstrated that composition of medical devices like dialyzer could impact BPA concentrations in controlled studies. Indeed, the occurrence of polycarbonate and polysulfone in dialyzer lead to overexposure of ESKDD patients (Mas et al., 2018; Murakami et al., 2007). Furthermore, several studies have highlighted BPA and ClxBPAs occurrence in dialysis fluids like dialysate but also in replacement fluid that is directly infused during an HDF treatment (Bacle et al., 2019, 2016; Hoekstra and Simoneau, 2013).

To our knowledge, no previous work has simultaneously evaluated BPA and ClxBPAs plasma concentrations in ESKDD patients during a dialysis session.

Thus, the first aim of our study was to compare BPA and ClxBPAs in ESKDD patients versus patients with stage 5 chronic kidney disease (CKD5) and healthy volunteers. The second aim was to describe the impact of a single dialysis session according to dialysis modalities of HD versus HDF and materials used with pre-post BPA and ClxBPAs concentrations.

2. Materials and methods

2.1. Clinical design and patient recruitment

We performed a pre-post study in a cohort of ESKDD patients, on thrice weekly 4 h chronic HD and HDF and CKD5 patients in the Poitiers University Hospital nephrology, hemodialysis, and transplant renal department. Eligible patients included were ≥ 18 years old, without guardianship or curatorship.

Healthy volunteers were non dialyzed patients from blood donations from the French Blood Establishment (FBE) of the University Hospital of Poitiers.

The study was conducted in accordance with the Declaration of Helsinki, approved by the French Ethics Committee (2016-A00475-48), and ESKDD patients, CKD5 patients and healthy volunteers gave their informed consent after being fully informed.

2.2. Plasma samples

For ESKDD patients, blood samples were collected routinely at a first mid-week dialysis session before and after dialysis session from the arterial blood using the slow flow method from the arterial line. To determine the impact of a single dialysis session on BPA and ClxBPAs concentrations, post-dialysis blood was also drawn similarly, just after the dialysis session.

For CKD5 patients, blood sample were collected during a consultation and for healthy volunteers, blood was drawn just prior to donation.

All blood samples were collected using lithium heparin tubes free of BPA to avoid contamination of target compounds. Samples were centrifuged and aliquoted in polypropylene tubes. Plasma samples were frozen at -80 °C until analysis.

2.3. Sample's analysis – assessment of BPA and ClxBPAs exposure

All solvents and reagents were of UHPLC grade and free of BPA and ClxBPAs. Polypropylene or glass materials were used to avoid BPA contamination. Human plasma, collected from multiple anonymous donors was used for the preparation of calibration standards in plasma and quality controls (QCs). BPA, Monochlorobisphenol A (MCBPA), 2,2'-dichlorobisphenol A and 2,6'-dichlorobisphenol A (DCBPA), trichlorobisphenol A (TCBPA) and tetrachlorobisphenol A (TTCBPA) were analysed in human's plasma using an offline solid phase extraction and injected into the UHPLC-MS/MS apparatus (API 6500 + mass spectrometer (ABSciex®, Concord, Canada)), according to a previous study (Cambien et al., 2020). Our work has focused on parent compounds, BPA and ClxBPAs because unconjugated BPA is assumed to be the form leading to toxic effects and ClxBPAs metabolism is still unknown (FAO/WHO Expert, 2010; Plattard et al., 2022). Briefly, 500 μ L of plasma was first spiked with 50 μ L of internal standard (IS) (BPA-d₁₆ and 2,2'-DCBPA-d₁₂). Then, 2.5 mL of water was added, and the samples were vortexed. The SPE procedure for clean-up samples was performed

using glass Oasis HLB® Cartridges (200 mg/5 mL Waters®, Milford, USA). Cartridges were conditioned with MeOH and then equilibrated with water. Samples were loaded on the wet cartridges, and then washed (MeOH/water, 30/70, v/v) and dried. Elution was performed with MeOH. Extracts were evaporated to dryness at 40 °C under a gentle nitrogen stream. Residues were dissolved ((MeOH/water 30/70, v/v) and vortexed for 10 s. Finally, 20 µL of extract were injected into the UHPLC-MS/MS apparatus. The UHPLC-MS/MS system consisted of an UHPLC system with an ACQUITY CSH C18 column (1.7 µm particle size, 2.1 mm × 100 mm, Waters®, Milford, U.S.A.) coupled to a Triple Quad Mass Spectrometer API 6500 + mass spectrometer (ABSciex®, Concord, Canada). This method of quantification had previously been developed and validated according to international guidelines (European Medicines Agency - Science Medicines Health, 2012).

Limits of quantification were set at the lowest level of calibration standard (0.1 ng/mL for BPA, 0.02 ng/mL for TTCBPA and 0.005 ng/mL for MCBPA, DCBPA and TCBPA). The limit of detection (LOD) was defined for each batch of analyses as three times the standard deviation of the mean peak area (n = 5) obtained using blank plasma samples (NORMAN, 2006). A compound was detectable in a sample if the peak area was greater than LOD. BPA was detected in plasma from anonymous donors used for standards and quality controls, however it was always at a level markedly lower than the limit of quantification (0.1 ng/mL) and has been considered in the calculation method. To summarize, the BPA/IS peak area ratio of blank plasma was daily subtracted from the BPA/IS ratio of each standard used to construct the calibration curve.

2.4. Clinical and biological variables

For ESKDD and CKD5 patients, age, gender, body mass index (BMI), diabetes; were recorded; routine biological data including creatinine, urea and albumin were collected at the start of dialysis session. For ESKDD patients, dialysis vintage, dialysis modalities (HD or HDF) and dialysis parameters including KT/V monitor and dialyzer type were recorded. The composition of dialyzers and the method used for their sterilization were analysed. Seven dialyzers (Polyflux 210 H, Theranova 500 (Baxter®, United-States); Vie 21 (Asaki, KASEI®, Japan); TS-1.6UL, TS-2.1SL, BK-2.1 F (Toray®, Japan) and Elisio 21 H (Nipro®, Japan)) have been used for the treatment of included patients. Dialyzer type has been separately analysed according to fibers composition: first group with polysulfone fibers (Vie 21, TS-1.6SL, TS-2.1SL) and the second one without polysulfone fibers (Polyflux 210 H, Theranova 500, BK-2.1 F and Elisio 21 H).

2.5. Statistical analysis

Quantitative variables were expressed as means ± standard deviations (SD); qualitative variables were presented as frequencies and percentages. Variables were compared by chi-2 test to compare qualitative characteristics of ESKDD and CKD5 patients. Student t test or Mann-Whitney test according to normal distribution were used to compare quantitative characteristics of ESKDD and CKD5 patients, BPA concentrations of ESKDD, CKD5 patients and healthy volunteers, and to compare the impact of dialysis modalities and materials used on BPA pre and post concentrations independently for ESKDD patients. We performed Kendall rank correlation analysis to evaluate correlation between variables. Finally, we performed a Wilcoxon rank sum test to study the impact of a single dialysis session on BPA concentrations with ESKDD pre-post dialysis concentrations and according to dialysis modalities and materials used.

Analyses were performed using R software (R Core Team, 2019). A two-sided alpha-level of 0.05 was chosen for statistical significance of all the analyses.

In the field of environmental health, variables with analytically non-detected or non-quantified values are commonly encountered. For

statistical analysis of detected but not quantified BPA, data were substituted for a fixed value: the limit of quantification (LOQ) divided by the square root of two ($LOQ/\sqrt{2}$) (Zoffoli et al., 2013).

3. Results and discussion

3.1. Sample's analysis

For each batch analysis, BPA contamination has been considered and three levels of quality controls were achieved for these five analytes. BPA and ClxBPAs determination were carried out only if contamination was controlled, QCs were < 20% for LOQ and < 15% for other QCs and linearity was demonstrated with correlation coefficient greater than 0.99.

3.2. Study process and patient characteristics

Sixty-four ESKDD patients, 36 CKD5 patients and 24 healthy volunteers were enrolled. For ESKDD patients, 32 were treated on HD (HD group) and 32 on HDF (HDF group). Demographic characteristics for all ESKDD and CKD5 patients have been summarized in Table 1.

Ages ranged from 37 to 89, from 36 to 88 and from 31 to 85, for CKD5, HD and HDF group, respectively. Twenty-two (61.1%), 20 (62.5%) and 22 (68.8%) patients were overweight or obese for CKD5, HD and HDF group, respectively. Creatinine was significantly higher in ESKDD patients versus CKD5 patients and albumin was significantly lower for ESKDD patients versus CKD5 patients. No significant difference was observed regarding ESKDD patients' characteristics treated by HD or HDF ($p > 0.05$).

3.3. Bisphenol A and chlorinated derivatives of bisphenol A chronic exposure in end stage kidney disease patients, chronic kidney disease patients and healthy volunteers

BPA distribution for healthy volunteers, for CKD5 patients and for ESKDD patients in pre-dialysis plasma samples in HD and HDF group are given in Fig. 1.

BPA was undetected, detected and quantified in plasma samples from healthy volunteers in 12 (50.0%), 8 (33.3%) and 4 (16.7%) samples, respectively, whereas it was undetected, detected and quantified in plasma samples for CKD5 patients in 17 (47.2%), 4 (11.1%) and 15 (41.7%) and it was quantified for all ESKDD patients' pre-dialysis samples. BPA plasma concentrations were 22.5 times higher for ESKDD patients in pre-dialysis samples versus healthy volunteers (2.208 ± 5.525 ng/mL versus 0.098 ± 0.169 ng/mL) ($p < 0.001$). CKD5 patients seem to be overexposed versus healthy volunteers, but it was not significant (1.606 ± 3.230 ng/mL versus 0.098 ± 0.169 ng/mL, 16 times higher concentrations). Finally, BPA plasma concentrations for ESKDD patients in pre-dialysis samples were 1.4 times higher versus CKD5 patients (2.208 ± 5.525 ng/mL versus 1.606 ± 3.230 ng/mL) ($p < 0.001$).

Regarding HD and HDF modalities, BPA pre dialysis were 20, and 25 times higher in pre-dialysis HD and pre-dialysis HDF versus healthy volunteers (1.983 ± 6.042 and 2.434 ± 5.042 versus 0.098 ± 0.169 ng/mL) ($p < 0.001$). For HD and HDF patients, BPA pre-dialysis concentrations were higher versus CKD5 patients (1.983 ± 6.042 and 2.434 ± 5.042 ($p < 0.006$) versus 1.606 ± 3.230 ng/mL ($p < 0.002$)). Finally, no difference was observed between BPA pre-dialysis in HD versus HDF group ($p > 0.05$).

For ESKDD and CKD5 patients we evaluated correlation between BPA and creatinine and between BPA and albumin levels. BPA levels were not correlated with creatinine (correlation coefficient $r = 0.126$; p -value = 0.06) or albumin levels ($r = -0.021$; p -value > 0.05).

ClxBPAs were assessed for healthy volunteers, for CKD5 patients and for ESKDD patients in pre-dialysis samples. For healthy volunteers, ClxBPAs were never detected or quantified. Results regarding CKD and

Table 1
Characteristics of end stage renal disease patients.

Characteristic	CKD5 patients (n = 36)	ESKDD patients (n = 64)	HD patients (n = 32)	HDF Patients (n = 32)	p-value CKD5 / ESKDD patients	p-value HD/ HDF
Male sex – n (%)	18 (50.0)	41 (64.1)	21 (65.6)	20 (62.5)	> 0.05	> 0.05
Age – yr.	67.2 ± 13.5	66.6 ± 11.9	68.3 ± 11.2	65.0 ± 12.6	> 0.05	> 0.05
Body-mass index*	28.1 ± 7.5	27.5 ± 6.1	27.1 ± 5.9	28.0 ± 6.3	> 0.05	> 0.05
Diabetes – n (%)	12 (33.3)	26 (40.6)	12 (37.5)	14 (43.8)	> 0.05	> 0.05
Dialysis vintage ≤ 3 yr. – n (%)	/	29 (45.3)	18 (56.3)	11 (34.4)	/	> 0.05
KT/V: monitor of dialysis	/	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.3	/	> 0.05
Double lumen dialysis catheter – n (%)	/	21 (34.4)	11 (37.9)	10 (31.3)	/	> 0.05
Creatinine – μmol/l	450.6 ± 126.5	683.5 ± 188.4	683.0 ± 168.5	684.1 ± 209.2	< 0.001	> 0.05
Urea – mmol/l	23.9 ± 6.1	22.1 ± 9.9	22.2 ± 7.0	22.0 ± 12.2	> 0.05	> 0.05
Albumin – g/l	41.3 ± 4.0	35.7 ± 4.0	35.9 ± 3.6	35.6 ± 4.5	< 0.001	> 0.05

Legend: Quantitative variables are expressed as means ± SD and qualitative variables as frequencies (n) and percentages (%). *The body-mass index is the weight in kilograms divided by the square of the height in meters.

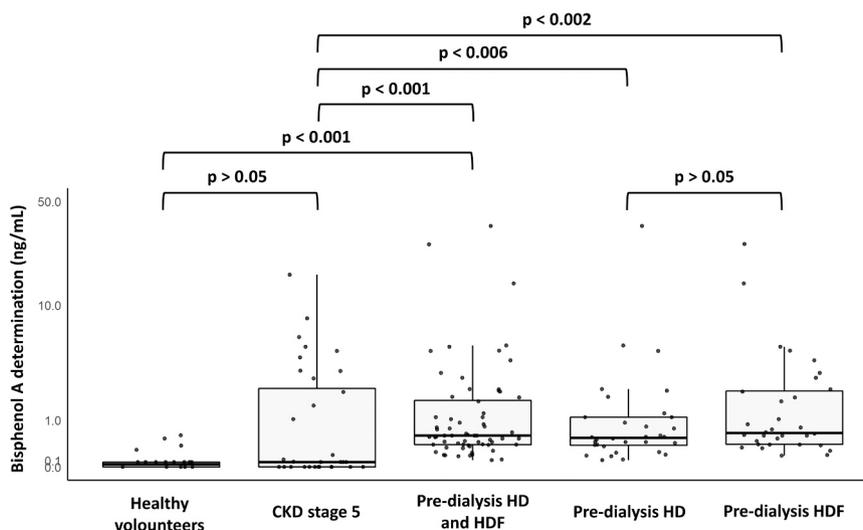


Fig. 1. : Bisphenol A concentrations measured for healthy volunteers, for chronic kidney disease patients stage 5 and for plasma pre-dialysis samples of patients with end stage kidney disease treated by dialysis (For a better visualization of the results, the ordinate scale is a logarithmic scale type log(1 + x)).

ESKDD patients are detailed in [Table 2](#).

For CKD5 and ESKDD patients, one ClxBPA at least has been detected or quantified in 14 patients (38.8%) and 24 patients (37.5%), respectively. Regarding all ClxBPAs, for CKD5 and ESKDD patients, they were detected or quantified in 21 times (14.6%) and 47 times (18.4%), respectively. MCBPA and DCBPA were the most quantified or detected in CKD and ESKDD patients with 8 (22.2%) and 16 (25.0%) samples for MCBPA, respectively and with 11 (30.6%) and 15 (23.4%) samples for DCBPA, respectively. Regarding HD and HDF modalities, ClxBPA were detected or quantified in 12 (37.5%) pre-dialysis samples for both modalities.

In our study we focus on unconjugated BPA, assumed to be the form leading to toxic effects whereas other studies evaluated total BPA (conjugated and unconjugated form) (FAO/WHO Expert, 2010; Mas et al., 2021; Quiróga et al., 2016). EDCs plasma levels were determined

using an UHPLC-MS/MS method, considered as a gold standard procedure (Fukata et al., 2006).

ESKDD patients were overexposed to BPA since BPA pre dialysis concentration in blood were 22.5 times higher than those measured for healthy volunteers. These results are in accordance with other previous studies that highlighted an overexposure of ESKDD patients (26.5 times higher) than healthy volunteers (Mas et al., 2018). Moreover, CKD5 patients seem to be overexposed to BPA versus healthy volunteers even if we did not find a significant difference. In our study BPA levels seems to be correlated with creatinine levels. All these results support the BPA accumulation with kidney disease (Krieter et al., 2013; Shen et al., 2019). Finally, ESKDD patients were overexposed to BPA (1.4 times higher) than CKD5 patients. Thus, this overexposure is due to dialysis therapy (Guimarães et al., 2023).

This exposure is not the only risk for ESKDD and CKD5 patients.

Table 2
ClxBPAs occurrence in chronic kidney disease patients and for patients with end stage kidney disease treated by dialysis in plasma pre-dialysis samples.

	CKD5 patients				ESKDD patients			
	MCBPA	DCBPA	TCBPA	TTCBPA	MCBPA	DCBPA	TCBPA	TTCBPA
Quantified - n (%)	2 (5.6)	4 (11.1)	0 (0.0)	0 (0.0)	6 (9.4)	5 (4.8)	5 (7.8)	2 (3.1)
Mean ± SD	0.008 ± 0.003	0.006 ± 0.001	/	/	0.084 ± 0.068	0.021 ± 0.022	0.078 ± 0.153	0.050 ± 0.028
Detected - n (%)	6 (16.7)	7 (19.4)	2 (5.6)	0 (0.0)	10 (15.6)	10 (5.6)	9 (14.1)	1 (1.6)
Non-Detected - n (%)	28 (77.7)	25 (69.5)	34 (94.4)	36 (100.0)	48 (75.0)	49 (76.6)	50 (78.2)	61 (95.3)

Legend: ClxBPAs are expressed as means ± SD and as frequencies (n) and percentages (%).

Indeed, for the first time, one ClxBPAs at least has been detected in 38 blood samples from ESKDD and CKD5 patients (38.0%) whereas they were never detected or quantified in healthy volunteers. Levels reported were lower than BPA. This result could be explained by occurrence of these compounds. Indeed, ClxBPAs are less frequently quantified than BPA in environmental samples and human biological matrix (Doumas et al., 2018; Grignon et al., 2016). Furthermore, no significant difference was observed between ESKDD and CKD5 patients. No data are available regarding ClxBPA toxicokinetic and metabolism, however we can assume that this exposure result from decreased renal function (Plattard et al., 2022). Further work are still needed to investigate ClxBPAs toxicokinetic (Andra et al., 2015a; Plattard et al., 2021; Riu et al., 2014). In a previous work, ESKDD patients were reported to be exposed to ClxBPAs via ultrapure dialysate and replacement fluid and HDF patients were at high risk due to infusion of replacement fluid (Bacle et al., 2019). However, in our study we did not find difference between ESKDD and CKD5 patients pre-dialysis samples and between HD and HDF pre-dialysis samples.

Regarding BPA toxicity, modulation of immune and inflammatory responses, disruption of neuroendocrine system, receptor pathways, inhibition of enzymes, epigenetic and genotoxic mechanisms lead to multi-organ damage. Thus, BPA induces relevant health effects covering developmental, reproductive and respiratory toxicity, but also metabolic, immuno, renal and hepatic toxicity and moreover carcinogenesis that can particularly affect elderly patients like ESKDD patients and patients with CKD5 (Ma et al., 2019). Regarding ClxBPAs, it has already been established that these derivatives have an estrogenic activity up to 38 times higher than BPA itself (Fukazawa et al., 2002). ClxBPAs exposure has been associated with significant health outcomes like myocardial infarction, particularly important for these ESKDD patients and patients with CKD5 because of their pathophysiology and existing co-morbidities (Andra and Makris, 2015; Hu et al., 2019; Neri, 2016). However, due to ESKDD patients' profile with multiple comorbidities, it is difficult to associate EDCs exposure with a health effect (Cambien et al., 2023). Indeed, clinical impact of BPA exposure on ESKDD patients requires specific studies with long-term biomonitoring and associated surveillance of blood pressure, cardiovascular risks, and monocyte cytotoxicity (Neri, 2016). To date, only one study found a relationship between dialysis, BPA exposure and health effects, with a positive correlation between diabetes and pre-dialysis BPA levels (Turgut et al., 2016). However, this study does not explain this correlation which could be due to other factors that dialysis therapy. Furthermore, our results highlight simultaneous exposure of patients with CKD5 and ESKDD patients to BPA and ClxBPAs. These simultaneous exposures could lead to combined toxicity named mixture or cocktail effects with synergistic activities and higher toxicity versus each compound toxicity studied

individually (Gaudriault et al., 2017; Kortenkamp, 2007). However, in the scientific literature, most *in vitro* and *in vivo* studies focus on one EDC at a time (Zhang et al., 2020; Gebru and Pang, 2023). Thus studies regarding cocktail effect are still critically needed, especially for chronic effects as presented in a review on combined toxicity of EDCs with effects on, thyroid hormone, stress, and immune system (Hamid et al., 2021). Thus, ESKDD patients and patients with CKD5 are a vulnerable population regarding EDCs with an increased risk of chronic diseases.

3.4. Impact of dialysis session and materials used on bisphenol A and chlorinated derivatives of bisphenol A plasma levels

The impact of the dialysis session on BPA concentrations was studied with pre-post and pre- and post-dialysis plasma concentrations. Results are shown in Table 3.

The impact of one single dialysis session could be investigated with pre-post concentrations. Regarding pre-post ClxBPAs, 64 ESKDD patients had at least one ClxBPAs detected or quantified in pre or post dialysis samples. Regarding these patients, 15 (23.4%) had an increased exposure (from undetected to detected or quantified; from detected to quantified), 29 (45.3%) had a decreased exposure (from quantified to detected or undetected; from detected to undetected) and 20 (31.3%) had stable exposure (from detected to detected; from quantified to quantified). Thus, dialysis therapy does not impact ClxBPA concentrations reported.

Regarding BPA, levels tended to increase during dialysis therapy with 2208 ± 5.525 ng/mL in pre-dialysis samples versus 5.568 ± 12.809 ng/mL in post-dialysis samples, respectively, but no statistical difference was observed (p -value > 0.05). These results highlighted the inability of a dialysis session to remove BPA from blood patients. Indeed, efficacy of dialysis session with KT/V monitor does not impact pre-post dialysis BPA concentrations ($p > 0.05$). Several studies have reported the same result (Bosch-Panadero et al., 2016; Krieter et al., 2013). Many reasons could explain this result. Unconjugated BPA is a small uremic toxin (228 Da) and can pass in both directions through the dialysis membrane during a session (Vanholder et al., 2003). Thus, BPA can be partially removed from blood to dialysate, but it can also be brought from backfiltration (dialysate to blood). Indeed, BPA is an ubiquitous substance transmitted by the different medical devices used in hemodialysis such as dialyzer fibers or housing, ultrafilters, dialysis concentrate and can also be found in ultrapure dialysate and replacement fluid (Bacle et al., 2016; Haishima et al., 2001). Furthermore, in our study BPA levels were not correlated to albumin levels. However, the majority of BPA is bound to protein such as albumin and thus, cannot be removed during hemodialysis. Hence, even if unbound BPA could pass from blood to dialysate during a dialysis session, BPA could also be transferred in the

Table 3
Impact of dialysis session and devices used on Bisphenol A plasma levels in end stage renal kidney disease patients treated by dialysis.

Variable - n (%)	Pre-dialysis BPA mean \pm SD (ng. mL)	p - value	Post dialysis BPA mean \pm SD (ng. mL)	p - value	p - value pre-post dialysis
Dialysis vintage					
≤ 3 years - n = 29 (45.3)	2.864 \pm 6.695	0.200	5.966 \pm 12.536	0.134	0.565
> 3 years - n = 35 (54.7)	1.665 \pm 4.357		5.239 \pm 13.204		0.342
Dialysis modalities					
Hemodialysis - n = 32 (50.0)	1.983 \pm 6.042	0.177	3.675 \pm 8.445	0.301	0.832
Online Hemodiafiltration - n = 32 (50.0)	2.434 \pm 5.042		7.462 \pm 15.960		0.488
KT/V monitor					
<1.2: poor - n = 27 (42.2)	3.162 \pm 7.979	0.596	3.352 \pm 10.171	0.805	0.170
≥ 1.2: good - n = 34 (53.1)	1.527 \pm 2.594		7.621 \pm 14.889		0.499
Dialyzer type					
Polysulfone free - n = 21 (32.8)	0.708 \pm 0.638	0.040 *	3.982 \pm 11.004	0.018 *	0.928
Non Polysulfone free - n = 41 (64.1)	3.054 \pm 6.770		6.629 \pm 13.932		0.683
Dialyzer sterilization					
Gamma-ray Irradiation - n = 51 (79.7)	2.611 \pm 6.131	0.191	6.034 \pm 13.246	0.467	0.765
Steam - n = 11 (17.2)	0.630 \pm 0.541		4.334 \pm 12.185		0.663

Legend: Variable are expressed as frequencies (n) and percentages (%) and BPA concentrations as means \pm SD.

other way from medical devices, from other body compartments such as adipose tissue or from release of protein bounded BPA (Csanády et al., 2002). Thus, pre-post dialysis BPA represents more an equilibrium between intake and elimination during a dialysis session and thus a global burden of BPA than only efficacy to clear BPA. The impact of dialysis session on BPA concentrations is therefore difficult to assess.

Regarding dialysis modalities, no statistical difference was observed between BPA mean concentrations in pre-HD versus pre-HDF or post-HD versus post-HDF and between pre-post HD or HDF (Table 3). HDF has been demonstrated to better remove small solutes (equivalent in our study to unconjugated BPA, minor form of BPA) but has no especially supplemental effect on clearance of highly protein-bound (equivalent in our study to BPA bound to albumin, major form of BPA) than HD (Krieter et al., 2010; Csanády et al., 2002). Our study confirms these observations since no significant difference was observed ($p > 0.05$). At the opposite, in other studies, HDF seems to reduce, unexpectedly, BPA levels in comparison to HD (Mas et al., 2018; Quiroga et al., 2016). This result could be explained by the possible loss of albumin during HDF leading to a decrease in the release of BPA by albumin and thus a decrease in unbound BPA concentrations (Weng et al., 2016; Vega et al., 2015). However, we did not report in our study albumin post dialysis concentrations. Finally, BPA and ClxBPAs environmental exposure due to HDF was established as higher than HD mainly due to infusion of replacement fluid (Bacle et al., 2019). However, regarding pre-post plasma levels, this overexposure was not confirmed in our ESKDD patient's treated by HDF. Finally, we reported important BPA values variability for ESKDD patients. A larger number of patients recruited would allow to consider this variability and possibly detect a significant difference in pre-post dialysis BPA concentrations according to parameters. Therefore, it is necessary to carry out further large-scale studies to assess these exposures and the risk for these vulnerable patients.

Regarding dialysis vintage, we did not observe significant difference in BPA concentrations between patients on dialysis for a short time (≤ 3 years) than for a long time (>3 years) (for pre-pre, post-post and pre-post values). Patients seem to be chronically exposed to a constant amount of BPA, but long-term dialysis exposure does not increase BPA concentrations. This result could be explained by the determination of BPA in only one single dialysis session. However, according to another study, ESKDD patients treated by dialysis therapy are overexposed to BPA but once the dialysis sessions has started, this exposure seems to be stable and does not increase with time, in accordance with our results (Krieter et al., 2013).

Regarding sterilization method, the SCENIHR highlighted the effect of sterilization on medical devices (Testai et al., 2016). In our study, sterilization method by gamma ray or steam does not modify BPA concentrations (for pre-pre, post-post and pre-post ($p > 0.05$)) whereas in another experimental study, migration of BPA with steam was multiplied by a factor of 2 to 5 versus gamma-ray sterilization in saline solution (Shintani, 2001).

Regarding dialyzer type, whether in pre- or in post-dialysis we observed significant differences in BPA determination regarding the presence of polysulfone in dialyzer fibers. Indeed, BPA determination in pre-dialysis samples was greater in plasma samples from the group with dialyzer fibers in polysulfone (3.054 ± 6.770 versus 0.708 ± 0.638 ; p -value = 0.040) and in post-dialysis samples (6.629 ± 13.932 versus 3.982 ± 11.004 ; p -value = 0.018) but we did not observe difference in pre-post dialysis samples. Thus, this overexposure occurs mostly after repeated treatments with polysulfone dialyzers and not just after one dialysis session (Mas et al., 2018). Polysulfone is recognized as one of the most BPA-releasing material (Testai et al., 2016). This result is in accordance with several studies that highlighted this overexposure with materials in polysulfone. At the opposite materials in cellulose and polynephron seemed to release less BPA (Bosch-Panadero et al., 2016; Mas et al., 2018; Murakami et al., 2007). Thus, the choice of materials used in the manufacture of these medical devices is significant. The French National Institute for Industrial Environment and Risks had

already highlighted alternative solutions, on his website and in a database, to substitute materials composed of Bisphenol A (INERIS - The French National Institute for Industrial Environment and Risks, 2021).

ESKDD patients seem to be overexposed to EDCs due to their pathophysiology with decreased urinary excretion and accumulation in the blood compartment (You et al., 2011), but also with their exposure during daily life and during dialysis treatment. In 2015, the SCENIHR has already warned of the dangers associated with chronic and significant exposure of population and more especially in ESKDD patients (Testai et al., 2016; SCENIHR). However, there are currently very few national or international regulations controlling the use of EDCs in the manufacture of medical devices, including those used in hemodialysis. Only one European regulations will require the manufacturer to provide the listing on the device itself and/or on the packaging of all substances considered as EDCs used in their manufacture in concentrations greater than 1% m/m as of May 26, 2021 (Regulation (EU), 2017). However, only a few substances have been officially defined as EDCs and thus practitioners will have to be vigilant in the concrete and real implementation of this regulation. Indeed, it has already been demonstrated that patients with hemodialysis therapy are also exposed to other pollutants not yet recognized as EDCs like Bisphenol F (BPF), contained in medical devices (Shen et al., 2019). Manufacturers must consider these issues and add these criteria in the choice of manufacturing materials used to reduce exposure of ESKDD patients. Practitioners in dialysis unit and pharmacists have a key role in ordering medical devices safe of EDCs to ensure ESKDD patients' safety.

Regarding this study, several limitations can be reported. Indeed, we did not collect the participants food intake in the three groups. However, diet can be a source of BPA exposure, and this may have influenced the BPA levels found (European Food Safety Authority (EFSA), 2015). Furthermore, in our study we decided to collect blood samples to avoid an additional invasive sampling. However, regarding chronic exposure, alternative matrix like hair could also be interesting to reflect EDCs exposure (Robin et al., 2022).

This work is to our knowledge the first to investigate, the impact of a dialysis session and materials used on BPA and ClxBPAs plasma concentrations and to compare these concentrations to those found in CKD5 patients and in control group. However, we did not focus on clinical outcomes for these patients. This aim could be investigated with further longitudinal cohort studies with larger sample sizes.

4. Conclusions

This study confirmed that ESKDD and CKD5 patients are overexposed to EDCs. These exposures must be considered due to their systemic properties and due to the cocktail effects induced by simultaneous EDCs in blood plasma samples. Newly regulation represents an important progress in this field to reduce ESKDD patients' exposure. However, manufacturer, practitioners in dialysis unit and pharmacists must be the driving force in the evolution of practices and composition of medical devices to protect these vulnerable patients. At the same time, further longitudinal cohort studies with larger sample sizes are required to assess clinical outcomes of EDCs exposure on ESKDD patients.

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CRedit authorship contribution statement

Guillaume Cambien: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Antoine Dupuis:** Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Visualization,

Writing – original draft. **Mohamed Belmouaz**: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft. **Marc Bauwens**: Conceptualization, Investigation, Validation, Writing – original draft. **Astrid Bacle**: Conceptualization, Validation, Writing – original draft. **Stéphanie Ragot**: Conceptualization, Formal analysis, Methodology, Validation, Writing – original draft. **Virginie Migeot**: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – original draft. **Marion Albouy**: Conceptualization, Methodology, Project administration, Validation, Writing – original draft. **Sarah Ayraud-Thevenot**: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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