Review Article

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Bisphenol (A) uremic toxin to take into account in the Renal disease in Hemodialysis

Bisfenol (A) una toxina a tener en cuenta en el enfermo renal en hemodiálisis

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Abstract

Introduction: Most uremic toxins are by-products of protein metabolism by action of intestinal flora. The metabolism of aromatic amino acids originates phenolic type residues. The most studied is p-cresol that is associated with renal function and vascular damage. Bisphenol A (BPA) is an exogenous molecule with characteristics similar to these aromatic uremic toxins. BPA is an estrogenic endocrine disruptor, found in tin cans, plastic bottles, epoxy resins and in some dialyzers. This molecule accumulates in patients who have impaired renal function. Observational studies have shown that exposure of BPA is linked to renal and cardiovascular injury, among many others in humans, and in animal studies a causal link has been described. Kidneys with normal renal function rapidly excrete BPA, but insufficient excretion in patients with CKD results in accumulation of BPA in the body.

Key words: Uremic toxin, Bisphenol A, chronic kidney disease, endocrine disruptor, hemodialysis.

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Resumen

Muchas toxinas urémicas son originadas como consecuencia del catabolismo proteico por la flora intestinal. El metabolismo de aminoácidos aromáticos origina residuos de tipo fenólico. De estas toxinas, la más estudiada es el p-cresol, que se asocia a la función renal y daño vascular. El Bisfenol A (BPA) es una molécula exógena de características semejantes a estas toxinas urémicas aromáticas. El BPA es un disruptor endocrino estrogénico que se encuentra en latas de conserva, botellas de plástico, resinas epoxi y en algunos dializadores. Esta molécula se acumula en pacientes que tienen deteriorada la función renal. Estudios observacionales han demostrado que una exposición a BPA está vinculada, entre otras muchas, a lesión renal y cardiovascular en los seres humanos; en estudios en animales se ha descrito un vínculo causal. Los riñones con función renal normal excretan rápidamente BPA, pero una excreción insuficiente en pacientes con ERC da lugar a la acumulación del BPA en el organismo.

Palabras clave: toxina urémica, bisfenol A, enfermedad crónica renal, disruptor endocrino, hemodiálisis.

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In Spain approximately 4 million people suffer from chronic kidney disease (CKD), of which 51,000 are in renal replacement therapy, half on dialysis and the rest with a functional renal transplant (Dialysis and Transplant Report 2012). Each year about 6,000 people with renal failure progress in their disease to the need to continue renal replacement therapy. The prevalence of CKD progressively increases with aging and with other diseases such as type 2 diabetes, arterial hypertension and atherosclerosis[1]. In CKD multiple molecules, called uremic toxins, are accumulated, which are responsible for the associated symptomatology and which contribute to an increase in morbidity and mortality. It is to be expected, therefore, that the elimination of uremic toxins will be accompanied by an improvement of the clinical situation.

Uremic toxins have been classified, according to size, into those of small size, with a molecular weight below 500 Da; of medium size, with a molecular weight between 500 and 5000 Da; and large, larger than 5000 Da[2]. However, regardless of their size, many of them are bound to a protein, which makes it difficult to eliminate them. Therefore, another way of classifying them is based on their union (or not) with proteins. Among the alterations directly related to uremic toxins are progressive loss of renal function, cardiovascular morbimortality and uremic symptoms, such as anorexia, vomiting, weakness, sleep disorders and neuropathy, among many others.

Among these toxins, there are some that, because they have an aromatic ring in their composition, are called aromatic (TUA). Particularly relevant in renal patients are the products originated by the metabolism of phenylalanine and tyrosine by intestinal anaerobic bacteria, such as p-cresol, phenyl acetic acid and phenols; or tryptophan degradation products that frequently lead to the formation of indoles as these accumulate in these patients because they cannot be eliminated by urine. These compounds, both free and in their conjugated forms in the form of sulfates or glucuronates, have been extensively studied due to their accumulation in patients with renal failure. There are other toxins with aromatic rings that have not been studied in relation to CKD, such as 1-methoxyiresorcinol, CMPF, hydroquinone, quinurenine, kynurenic acid or 3-hydroxyquinurenone.

Bisphenol A (BPA) is among the uremic toxins that accumulate in the renal patient and may influence his clinic. It is a synthetic estrogen that is part of multiple plastics commonly used and is part of the group of molecules that are called endocrine disruptors to be able to alter the homeostasis of processes such as reproduction, weight and development. BPA acts as a hormone and can alter cellular function at very low concentrations. The levels of this molecule increase in the renal patient, since its elimination is mainly given by the renal route. BPA is an environmental toxicant that has phenolic rings and structural similarity to phenols, although the origin of both molecules is different. However, the metabolism and side effects of BPA have common characteristics with intestinal phenols.

In the present review we analyze BPA as a urogenic toxin of exogenous origin, included in the group of phenols. Although it is a molecule whose toxicity has been widely studied, its use has not been prohibited because it is completely eliminated by the urine. However, the molecule in question draws the attention of the nephrologist especially since it is related to several renal alterations and because, having renal elimination, it increases in the blood and tissue levels of the uremic patient.

Aromatic Toxins

The origin of uremic toxins is multiple. Some originate in the endogenous metabolism, others in the microbial metabolism and others, finally, come

from an exogenous source. Most of the uremic toxins originate in the endogenous cellular metabolism of the individual. However, the importance of toxins generated by intestinal microbial metabolism is increasingly recognized[3]. Also toxins from the diet have an important role, such as oxalate and advanced products of glycoxylation[4]. It should be mentioned that uremic toxins accumulate progressively as renal function decreases.

Phenols and indoles are the most studied protein-bound uremic toxins. It is recognized the direct involvement of both in the progression of renal failure and vascular damage. These toxins are metabolites of protein catabolism by intestinal bacteria, which shows a high increase in the patient with CKD.

Daily the intestine reaches up to 4 gr. of nitrogen in the form of proteins (50%) and peptides (20-30%). These proteins are degraded by proteases and peptidases to amino acids. Part of these reaches the colon, where it is degraded by intestinal bacteria giving rise to potentially toxic metabolites such as ammonium, amines, thiols, phenols and indoles. These products of colonic putrefaction are eliminated almost entirely by feces, although a part is absorbed[5].

Phenols include p-cresol and p-cresylsulfate; phenyl-acetic acid and phenol[6].

- P-Cresol, p-Cresylsulfate, and p-Cresol glucuronide: p-cresol is a product of the metabolism of phenylalanine and tyrosine by intestinal anaerobic bacteria. Most p-cresol is conjugated by the flora in the intestinal wall to p-cresylsulfate and in the liver to p-cresylglucuronide. Most p-cresol circulates as p-cresylsulfate[7], a molecule that is a potent oxidant. Free (i.e., non-protein bound) p-cresol is related to cardiovascular damage in non-diabetic patients and increased cardiovascular mortality[8]. However, the method of measurement of p-Cresol did not distinguish p-cresol as such from the conjugated form as p-cresylsulfate, of which toxicity, in addition, there is evidence6.
- Phenol comes mainly from direct intake; the catabolism of tyrosine and other substrates by intestinal bacteria; And tobacco use.
- Phenyl acetic acid is the result of the degradation of phenylalanine. It binds in 30% of said acid to proteins. It has been related to alteration of immunoregulation in the uremic patient, while participating in oxidative stress[9] and inhibiting the function of the osteoblast contributing to bone alterations[10].

Of the indoles we should highlight indoxylsulfate and indoleacetic acid. Indole is a heterocyclic aromatic structure found in many organic compounds such as tryptophan and its metabolites. Intestinal bacteria, by degrading tryptophan, generate indole and indoleacetic acid. Indole is subsequently sulfated by hepatic enzymes to indolsulfate. It should be mentioned that these metabolites increase in cases of renal failure.

- Indoxylsulfate: it is the most studied of indoles and is a renal and vascular toxin. In hemodialysis, it is associated with atherosclerosis[11], vascular calcification and endothelial dysfunction[12]. It has also been implicated in the progression of renal disease by impairing cellular antioxidant capacity and by being a pro-inflammatory and profibrotic molecule[13].
- Indoleacetic acid: has been associated with progression of renal interstitial fibrosis[14].

Main complications arising from the accumulation of uremic toxins of intestinal origin

Uremic toxins derived from the decay of proteins by colon bacteria, such as phenols and indoles,

have been linked to multiple clinical alterations in the CKD patient. Among them we could highlight:

a) Progression of chronic renal failure: both indoxylsulfate and p-cresyl sulfate have been associated with impaired renal function, since it accelerates the progression of the disease[15]. In a prospective study with 268 patients with CKD at various stages, the concentrations of both molecules were predictive of the progression of renal disease, independently of other cardiovascular risk factors[16].
b) Cardiovascular complications: a relationship between indoxylsulfate concentrations and vascular damage has been observed, as well as aortic calcification, which directly implicates this molecule in the cardiovascular damage of the uremic patient[17]. The indoxylsulfate is also involved in the oxidative stress of endothelial cells and in the proliferation of vascular smooth muscle cells[18]. In addition, it has a profibrotic effect and increases hypertrophy of the cardiac fibroblasts[19].
c) to renal patient anemia by interfering with adequate production of erythropoietin[20].
d) Osteodystrophy: indoxylsulfate has adverse effects on bone formation by promoting oxidative stress in osteoblasts and inducing resistance to PTH, with the development of an adynamic bone[21].

Bisphenol A as uremic toxin

BPA Overview

In the last few years, the scientific community has received great attention from the harmful effect of an environmental toxicant, phenolic type, bisphenol A (BPA). In particular, it has also generated interest among the nephrological community as it has been associated with renal and endocrine alterations, but mainly because its elimination is renal and, therefore, the blood and tissue levels of this toxic one are increased in the renal patient.

BPA is an ingredient of plastic polycarbonate and epoxy resins, which adds hardness, clarity and light weight, while resisting both temperature and electricity. BPA was synthesized in the 1930s as synthetic estrogen[22]. The occurrence of diethylbestrol at the same time displaced this type of research until it was discovered that BPA acted as a stabilizer in the production of plastic polycarbonates[23]. Plastic polycarbonates are used in containers and containers commonly used in the food industry and in the home, such as plastic bottles, baby bottles, lenses, medical devices, etc. BPA-containing epoxy resins are used as a coating on food and beverage cans. However, due to the possible health impact, the epoxy coating was replaced in Japan by a polyester film[24]. BPA is also used in the synthesis of polysulfones, in polyether ketones, as an antioxidant in some plasticizers and as an inhibitor of polymerization in the PVC.

BPA is a special case of uremic toxin since its contribution is exogenous, unlike the toxins normally considered. Although it is a ubiquitous compound, it is mainly found, as mentioned, in plastic bottles, baby bottles, lenses or medical utensils (dialyzers). BPA-containing epoxy resins are used as a coating for cans used in feed, although, it is said, there is a tendency for their substitution by polyesters[24]. Given its widespread use, regulatory agencies have for many years debated the potential risk of BPA as a synthetic estrogen for daily human consumption for human health.

BPA usually passes into the bloodstream through the oral route, usually accompanying the products contained in plastic containers that include it among its components. As with phenols of intestinal origin, BPA is conjugated in the intestine and liver with glucuronic acid and is almost completely eliminated by urine[25].

There may also be non-oral exposure to BPA, so it is also considered an environmental toxicant. However, the continued exposure of the public to this toxin raises more controversy because of its role as an endocrine agonist. Although BPA is commonly classified as an endocrine disruptor, the European and American authorities consider that because of its rapid elimination it can be considered a relatively safe compound in spite of the published evidence[26].

BPA in chronic kidney disease

As mentioned, BPA under normal conditions is metabolized in the liver and eliminated by the urine. Studies reveal that urinary excretion of BPA can be used as a biomarker for renal disease[27], because urinary excretion of BPA decreases with impaired renal function and these associations differ according to age or sex. The study also reveals a correlation between BPA excretion and glomerular filtration (GFR) [28-30].

Published studies on BPA and patients with CKD observe that there is an increase of BPA in blood. Patients with a decrease in renal function had an increase in serum BPA and in patients on hemodialysis levels were even higher[31]. One of the arguments used by government agencies to consider the use of BPA in the general population is the almost complete urinary elimination of the conjugate molecule[32], which reduces the risks of exposure to BPA. For all of the above, patients with renal disease are the subject of special study because they are more sensitive to the accumulation of BPA and its potential toxicity due to the loss of physiological mechanisms of excretion of BPA in urine.

Kretier and colleagues observed that as GFR declines, serum levels of BPA increased[33]. In our study, we demonstrated that serum levels of BPA in dialysis patients without residual renal function are much higher than control patients with residual renal function. This confirms the previous studies that observe that the inability to excrete BPA by urine results in an increase of the serum values of BPA33. Kanno et al. Observed that in patients on hemodialysis the concentration of BPA (5.3 ± 0.3 ng/mL) is higher than in patients on peritoneal dialysis (3.8 ± 0.2 ng/mL) and higher than in patients with hemodialysis (2.6 ± 0.1 ng/mL)[34]. The renal patient should therefore not be included in the general provision according to which BPA is non-toxic when removed by the kidney, as it has altered this route of elimination. Therefore, it would be in agreement with the recommendations to take care of exposure to BPA in patients with CKD[35]. However, as we have already mentioned, in this group there would be 10% of the Spanish population, a good part of which does not know to present the disease and, therefore, accumulates the BPA in blood and, possibly, in tissues.

Among the indications that point to a causal role of BPA in renal disease, it is necessary to consider that, in healthy adults, urinary BPA levels> 1.4 µg/L are associated with a 23% higher risk of micro albuminuria than in adults And children with levels <0.5 µg/L29. It has also been associated with the presence of low grade albuminuria in Chinese adults[36]. Possible mechanisms of BPA-mediated nephrotoxicity related to an increase in oxidative stress, inflammation and induction of arterial hypertension have been identified[37, 38]. In addition, serum BPA has recently been shown to be a predictor of renal disease progression in patients with type II diabetes[39], in the sense that patients with higher levels of BPA have a greater progression of their renal disease. It has been shown that BPA reduces antioxidant activity, which should contribute to oxidative stress19; also that BPA reduces podocyte viability[37] and is capable of producing podocyte hypertrophy, since it involves GFR-β and cyclin kinase inhibitor

p27kip1, which is known for its role in the mechanism of renal cell hypertrophy[40-42].

However, the accumulation of this substance in the patient with a decrease in glomerular filtration has motivated the analysis of the same as a possible uremic toxin. Among the arguments put forward by the various official bodies to consider the use of GAP in regular use as safe is, as mentioned, almost complete elimination by urine of the conjugate molecule[32]. For this reason, patients with renal damage, in whom the removal of the molecule is altered, should be considered a population especially sensitive to BPA.

The greater progression of renal disease this feedback loop would increase, as patients with CKD are not able to completely excrete BPA in the urine43, which may influence the deterioration of renal function[31]. However, the National Health and Nutrition Examination Survey 2003-6 (NHANES III), on a sample of 2573 patients, also observed a decrease in the elimination of BPA with impaired renal function, although this case was only significant in women[29]. On the other hand, in the study of Krieter a correlation between the deterioration of the renal function and the plasma concentrations of BPA[33] is observed.

Bisphenol A on dialysis

The patient on dialysis is a patient with a special risk of BPA toxicity, since renal elimination is completely abolished. Additionally, in patients on hemodialysis, BPA, being a ubiquitous component, forms part of the plastic composition of some dialyzers and common use lines, both in the form of polycarbonate in the shells, and in multiple membranes of Dialysis, such as polysulfones (PS) or Polyester-Polymer alloy (PEPA).

In these dialyzers the polymer is in constant contact with the blood, which would give rise to its release into the bloodstream. For this reason, the increase of the toxin in the hemodialysis patient is not only due to an environmental exposure, but possibly to the technique used in the procedure[44]. Different studies have described that effluents from dialyzers composed of these materials have high concentrations[31].

H. Shintani et al. analyzed four types of polysulfone dialyzers on the market, with a polycarbonate or butadiene-polystyrene copolymer shell and with sterilization with steam or gamma rays. The BPA increases more in dialyzers with polycarbonate casing, regardless of the membrane. Polyisulfone dialyzers with a water vapor-sterilized polycarbonate casing are the ones with the highest BPA level detected in the effluent[45]. Similar findings have been found by other authors[46].

These studies show that the migration of BPA into the dialysers when blood is used is significantly greater than when saline is used. Possibly, this difference is due to the effect of hydrophobic components in the blood, such as lipids and lipoproteins. Thus, the concentration of BPA in the effluent of a liquid on a polysulfone membrane is different if the flow on it is water or coil serum (eluting 3.78-141.8 ng vs. 140.7 2090 mg per dialyzer) [44].

The flow would also affect the amount of BPA extracted, due to residence time in the dialyzer. Therefore, although it is very difficult to determine in these patients if the plasma concentrations exceed those recommended, most authors recommend using dialyzer dialysis patients with a lower BPA and also try to avoid BPA-rich plastics, such as bottles.

There are no well-designed studies on the involvement of techniques with great convective transport, such as hemodiafiltration. Although it is a te-

chnique that can purify the BPA, it is not less true that a reinfusion liquid is used that crosses membranes with BPA, reason why it could be increasing its infusion. It will be necessary to determine their involvement in prospective and cross-over studies to observe what happens in this treatment modality.

On the contrary, in PD there is only one study about the impact of BPA, finding that its concentration in the dialysis fluid is much lower than the permitted level. Although they only study it in 4 patients, it only seems to increase the concentrations of BPA in a patient. Therefore, the authors conclude that BPA does not appear to be purified or increased with DP[47].

The newly found evidence led the Scientific Committee of the European Union (Scientific Committee on Emerging and Newly Identified Health Risks) to issue, in early 2015, a report entitled "Final opinion on the safety of the use of bisphenol A in medical devices" in which they conclude that there is a risk of adverse effects derived from BPA when it is available systemically via non-oral exposure routes, especially for infants in intensive care units, children undergoing prolonged medical procedures or patients on dialysis[48].

Despite this certainty, there are practically no long-term prospective studies linking the effect of hemodialysis with the presence of BPA and its possible effects. In 2013, Krieter et al studied the effect of hemodialysis over a 4-week period, concluding that the differences between the membranes with bisphenol (polysulfone) and without bisphenol (polynephron) were not significant33. However, the fact that the casings of all the dialyzers used contained BPA and the short time considered by the study could explain these results.

Our group, on the other hand, used a prospective and crossed design, exchanging dialysers with BPA (polysulfone) and without BPA (polynephron) for 3 months each. Mean levels of BPA increased after a single session using polysulphone dialyzers, while they did not vary in those dialyzed with polynephron. Also, the chronic use of dialysers with polysulfone membrane caused an increase in serum levels of BPA, which is not observed in polynephron[49]. The average levels of BPA increased after a single session using polysulfone dialyzers, whereas they did not vary in those dialysed with polynephron.

Also the chronic use of dialysers with polysulfone membrane caused an increase in serum levels of BPA not seen in polynephron. The determination of BPA in circulating cells gave rise to similar results and, in the period studied with polysulfone dialyzers, resulted in an increase, whereas in the case of the polylinephrine levels of BPA decreased in a period of time of 3 months. This increase was associated with both increased intracellular free radical levels and circulating inflammatory markers (IL-6, TNF-α, C-reactive protein) in patients, as well as in in vitro assays using circulating cells, in which that the polysulfone membranes release bisphenol into the medium and this results in an increased production of cytokines in cultured lymphocytes.

This is the first prospective study to evaluate the impact of BPA-free dialyzers, so prospective studies are required to assess whether observed increases in BPA and its effects on increased oxidative or inflammatory stress are associated with a worse clinical prognosis in these patients.

In summary, bisphenol A is a synthetic estrogen that is found to be part of everyday plastics and hemodialysis material, such as some membranes. It is eliminated by the kidney, so it accumulates in the kidney patient. Its molecule is similar to other uremic ring-borne toxins, such as pCresol, which are

well studied for having a significant role in the renal patient's morbidity and mortality. The metabolism and relationship with inflammation and oxidation are very similar between both. Although there are still outstanding questions, such as knowing the tissue concentration of BPA in the patient on hemodialysis, there is evidence to avoid bisphenol A in these patients. The European Union's expert report, set out in the SCENIHR report, defends this position[48,50]. We therefore consider that bisphenol A should be considered an exogenous uremic toxin.

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Conflict of interests

The Nephrology Laboratory has received a grant from Nipro Corporation to investigate the effects of bisphenol in renal patients. However, this company has not participated in the design of the study, interpretation of the results or writing of the manuscript.

Ethical Responsibilities

Protection of people and animals

The authors state that no human or animal experiments have been performed for this research.

Confidentiality of data

The authors state that no patient data appears in this article.

Right to privacy and informed consent

The authors state that no patient data appears in this article.

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