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ASSESSMENT OF SERUM BİSPHENOL-A CONCENTRATİONS AND PROTEİNURİA LEVELS İN PATİENTS WİTH PROTEİNURİA

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ABSTRACT

Objective: Bisphenol A (BPA) is a primary raw chemical utilized predominantly in the manufacturing of plastics. BPA exhibits inflammatory and nephrotoxic effects on the organism. This study examined the correlation between serum BPA and proteinuria. **Methods:** A total of 40 patients with stage 1 and 2 chronic kidney disease (CKD) and proteinuria, devoid of structural renal abnormalities, who came to a tertiary healthcare center from October 2019 to October 2020, were included, along with a control group of 35 patients. **Results:** Upon examination of the data between the two groups, the median age of the patient group was found to be 39 years (range 19-65), whereas the median age of the control group was 32 years (range 24-58). The groups exhibit no disparity for gender and age. (with p=0.8 and p=0.6, respectively). The GFR level was 92.09±22.35 in the proteinuric cohort and 105.74±10.2 in the control cohort. The creatinine concentration was 0.90±0.26 mg/dl in the proteinuric cohort and 0.79±0.15 mg/dl in the control cohort. The PRCR levels were 1382 mg/g (range 123-4338) in the proteinuric group and 87 mg/g (range 38-307) in the control group. Substantial disparities were seen among the groups (p=0.001, p=0.048, and p=0.001, respectively). BPA concentrations were measured at 1.38 ng/ml (0.51-14.50) in the proteinuric group and 4.93 ng/ml (0.56-14.50) in the control group (p=0.08). **Conclusion:** Serum BPA concentrations were correlated with GFR levels. Concerns have been expressed regarding the potential for BPA exposure to induce clinically significant alterations in kidney function, linked to exposure to prevalent environmental contaminants at existing levels.

KEYWORDS: chronic renal disease, bisphenol A, glomerular filtration rate, proteinuria.

INTRODUCTION

Exposure to diverse chemicals is a prevalent issue in contemporary culture. These compounds encompass BPA, utilized in the manufacture of epoxy resins and polycarbonate plastics.[1] BPA is extensively utilized in various applications, particularly in containers and infant feeding bottles. Approximately 6 million tons of BPA are generated globally.[2] BPA was identified in the urine samples of more than 90% of adults in the United States, and in a study conducted in Spain, it was present in 97%

of participants.[3-4] The primary pathway for BPA absorption into the body is oral, although it can also be inhaled through the respiratory tract.[5] Moreover, groundwater and natural water sources are contaminated with BPA, exacerbating environmental damage.[6] BPA, owing to its estrogenic characteristics, is recognized for inducing obesity, insulin resistance, thyroid and hepatic dysfunction, and nephrotoxicity.[7] A 2008 study by Lang et al. revealed that elevated urinary BPA levels in patients with type 2 diabetes mellitus (T2DM) correlated with an increased risk of cardiovascular disease.[8]

BPA is conjugated with glucuronic acid in the liver, resulting in the loss of its estrogenic activity, and is then eliminated through the intestines.[9] BPA and its metabolites are eliminated in urine. Consequently, serum BPA concentrations are elevated in individuals with COPD. A negative connection was identified between GFR and serum BPA levels.[10] Research has indicated a rise in plasma BPA levels in chronic kidney disease (CKD). The greatest BPA content was seen in patients with Stage 5 CKD.[11] Proteinuria is characterized by the presence of over 150 mg of protein in a 24-hour urine sample, an albumin/creatinine ratio exceeding 30 mg/g in a spot urine sample, and a protein/creatinine ratio surpassing 150 mg/g.[12] Podocyte hypertrophy is prominent in glomerular disorders, resulting in a diminished podocyte count and a reduction of nephrin and podocin proteins in the slit diaphragm, which leads to proteinuria.[13] BPA diminishes the expression of nephrin and podocin proteins. BPA-injected animals exhibited elevated urine albumin excretion, podocyte hypertrophy, and glomerular mesangial enlargement.[14] These findings elucidate the mechanisms of BPA in proteinuria.

Literature reviews indicate that studies on serum BPA levels concerning kidney function have predominantly focused on animal models or chronic kidney disease (CKD) rather than proteinuria.[10-14] This study seeks to assess the correlation between blood BPA levels and the extent of proteinuria in patients exhibiting proteinuria.

MATERIALS AND METHODS

A tertiary health facility enrolled 40 patients with proteinuria and a control group of 35 patients in the trial conducted from October 2019 to October 2020.

Criteria for Inclusion

Individuals aged 18 years and older with stage 1 and 2 chronic kidney disease, possessing a glomerular filtration rate (GFR) exceeding 60 ml/min and lacking structural renal abnormalities, including both proteinuric patients and healthy volunteers, were incorporated.

Criteria for Exclusion

Patients exhibiting proteinuria due to conditions such as diabetes and hypertension, individuals with stage 3-5 chronic kidney disease, those diagnosed with malignancies, participants who engaged in strenuous exercise within the preceding 24 hours, individuals with urinary tract infections, and patients with a history of proteinuria were excluded from the study.

Examination Procedure The main objective is to assess the impact of serum BPA concentrations on the quantity of proteinuria. The secondary endpoint is the alteration in GFR level. Seventy-five persons who met the criteria were identified. A control group was established from patients attending the nephrology outpatient clinic with various complaints.

A daily total protein excretion beyond 150 mg in a 24-hour urine collection is classified as proteinuria, based on quantitative measurement. The estimated glomerular filtration rate (GFR) was computed utilizing the Modification of Diet in Renal Disease (MDRD) model. The GFR in mL/min/1.73 m² was computed using the formula: 175 x SerumCr^-1.154 x age^-0.203 x 1.212 (if the patient is Black) x 0.742 (if female).[15] The phases of chronic kidney disease (CKD) were established in accordance with the KDIGO 2012 guidelines. Stage 1 CKD is categorized as a GFR of 90-120, stage 2 CKD as 60-89, stage 3a CKD as 45-59, stage 3b CKD as 30-44, stage 4 CKD as 15-29, and stage 5 CKD as less than 15.[16] Serum BPA levels were assessed with the Human BPA ELISA kit (sensitivity: 0.23 ng/ml, measurement range: 0.5 ng/ml – 200 ng/ml, inter-assay variation: CV < 10%, intra-assay variation: CV < 8%) via the ELISA method. Measurements were assessed using an ELISA reader at a wavelength of 450 nm ± 2 nm. Urine samples were obtained from patients on the same day for the assessment of spot urine protein/creatinine ratio (PRCR). Patients with proteinuria were defined as those with PRCR over 150 mg/dl.

Ethical approval for this study was secured from the University of Health Sciences Bursa High Specialization Training and Research Hospital, under decision number 2011-KAEK-25 2019/10-18.

Statistical analysis

The analysis of the study data was conducted using IBM SPSS Statistics 23 software. Initially, descriptive statistics and the normality distributions of the data were analyzed.

In relationship analyses, the Mann-Whitney U Test was employed to compare categorical variables, while the Independent Samples T-Test was utilized to assess significant differences between the means of independent groups, given the data exhibited a normal distribution. During the analysis, instances with a p-value below 0.05 were deemed statistically significant.

RESULTS

Table 1 presents a comparison of demographic factors between the proteinuric group (Group 1) and the control group (Group 2). The groups have comparable distributions concerning gender and age.

Comparison of BPA levels between Group 1 and Group 2

Table 2 indicates that BPA concentrations were 1.38 ng/ml (0.51-14.50) in the proteinuric cohort and 4.93 ng/ml (0.56-14.50) in the control cohort. The BPA levels exhibited no significant difference between the groups (p=0.08).

Comparison of glomerular filtration rate data between group 1 and group 2

Table 2 indicates that GFR levels were 92.09±22.35 in the proteinuric group and 105.74±10.21 in the control group. The GFR value of the first group was significantly lower than that of the control group (p = 0.001).

Comparison of creatinine concentrations between group 1 and group 2

Table 2 indicates that creatinine levels were 0.90±0.26 mg/dl in the proteinuric cohort and 0.79±0.15 mg/dl in the control cohort. The creatinine level in the first group was significantly elevated compared to the control group (p = 0.048).

Comparison of PRCR values between Group 1 and Group 2

Table 2 indicates that PRCR levels were 1382 mg/g (range: 123-4338) in the proteinuric group and 87 mg/g (range: 38-307) in the control group. The PRCR value of the first group was determined to be superior to that of the control group. p = 0.001.

Table 1: Demographics.

	Groups		p
	Patient (n=40)	**Control (n=35)**	
Age(years)	39(19-65)	32(24-58)	0,062[a]
Sex			
Female	22(%55)	20(%57,10)	0,852[b]
Male	18(%45)	15(%42,90)	
ACEi/ARB			
Yes	33(%82,50)	0	**<0,001[b]**
No	7(%17,50)	35(%100)	

[a] Mann–Whitney U Test; [b] Chi-square Test

ACEi: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers

Table 2: Assessment of Bisphenol A and additional laboratory metrics.

	Patient	Control	p
Bisphenol A(ng/ml)	1,38(0,51-14,50)	4,93(0,56-14,50)	0,083[a]
PRCR(mg/g)	1382(123-4338)	87(38-307)	**0,001**[a]
BUN(mg/dl)	15(7-33)	13(8-25)	0,343[a]
Creatinin(mg/dl)	0,90□0,26	0,79□0,15	**0,048**[c]
GFR	92,09□22,35	105,74□10,21	**0,001**[c]

PRCR: Protein/Creatinine ratio; BUN: Blood Urea Nitrogen [a] Mann–Whitney U Test; [c] Independent Samples t-Test

DISCUSSION

This study aims to evaluate the relationship between serum BPA levels and the amount of proteinuria in patients with proteinuria. In the proteinuric group, there is a difference in GFR, PRCR, and creatinine levels compared to the control group. Proteinuria is also used in the classification of CKD along with GFR.

Proteinuria is an indicator of early kidney disease.[17] The degree of proteinuria is associated with disease progression.[18] Among the causes of proteinuria are diabetic nephropathy, drug-induced nephropathy, infections, and chemicals.[19] There are inconsistencies among studies showing that BPA, a chemical substance, is a risk factor for proteinuria.

Malits J and colleagues detected lower urinary BPA levels in the KBH population compared to the healthy group and found no association between BPA and proteinuria.[20] Your L. and her friends, on the other hand, found that proteinuria increased as the amount of BPA in urine increased.[21] In our study, no difference was found between the groups in terms of proteinuria with serum BPA levels. Among the reasons for this is that exposure estimation based on urinary excretion may not be valid in CKD. In KBH, urinary output is low, but it is unclear whether this condition developed secondary to BPA exposure or whether urinary output decreased as a result of increased BPA retention. Additionally, existing studies have assessed BPA exposure by evaluating urinary BPA.[20-21] The evidence is observational and definitive conclusions about causality cannot be reached. In the results of our study, no consistency was found between BPA levels.

When kidney function is normal, serum BPA is almost undetectable. It has been reported that the average BPA levels in patients with chronic kidney disease are 0.23 ng/mL.[22] In another cross-sectional study on chronic kidney disease, plasma BPA levels began to rise in patients with CKD stage 3, which is consistent with the early-stage CKD examined in our study.[23] In our study,

higher BPA was detected in the control group, which differed from existing studies.

In its 2015 assessment of BPA, the European Food Safety Authority (EFSA) reduced the tolerable daily intake (t-TDI) value from 50 µg/kg to 4 µg/kg.[24] The reference point for the critical human dose was set at 8.2 ng/kg daily. In 2023, the new t-TDI value of 0.2 ng/kg per day was determined by adjusting the t-TDI value with an additional uncertainty factor. In our study, patients' body measurements were not recorded, but the serum BPA value in the control group was 4.93 ng/ml, which was found to be significantly higher than the human body weight-based value of 0.2 ng/kg.[25] In 2011, the European Union banned the use of BPA in the production of baby bottles and later banned BPA in food packaging for children up to three years old.[26]

It is believed that the differences in GFR, creatinine, and PRCR values are due to natural variations in the selection criteria of the groups, rather than the effect of BPA levels.

After BPA exposure, effacement of podocytes was observed under light microscopy on glomerular epithelial cells.[27] It also showed renal proximal tubular damage in the groups treated with BPA.[28] It was concluded that renal tubular dysfunction following BPA exposure is a result of both glomerular and tubular dysfunction. Oxidative stress is an imbalance between the production of reactive oxygen species and antioxidant defenses, leading to oxidative damage. BPA exposure causes a decrease in GFR by creating oxidative stress. BPA was found not only to increase the oxidant molecule nitric oxide (NO) but also to decrease the antioxidants glutathione (GSH) and the enzyme superoxide dismutase (SOD) in kidney tissues. This imbalance has led to renal oxidative stress and subsequent renal oxidative damage, as evidenced by an increase in malondialdehyde (MDA), an index of lipid peroxidation.[29]

This study has some limitations; daily or cumulative exposure could have been examined by including body mass index (BMI) in the study. Including more patients will increase generalizability. BPA levels could have been examined in urine tests in addition to serum, and their relationship with renal parameters could have been analyzed. In nephrotoxic patients, by reducing BPA exposure, a clearer assessment of the reversibility of the damage will yield more definitive results. The study could have been further expanded to include patients from every stage and those receiving renal replacement therapy.

CONCLUSION

Serum BPA levels were shown to be correlated with GFR levels. Exposure to BPA raises concerns regarding the possibility for clinically significant alterations in kidney function, linked to exposure to prevalent environmental contaminants at existing levels.

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