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Bisphenol A and Coronary Artery diseases: An epidemiological, laboratory, and clinical study

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Abstract

Bisphenol A (BPA) is one of the world's highest production volume endocrine -disrupting chemicals which has generated the greatest amount of interest and controversy. It has been determined that the primary cause of death in both industrialized and developing nations is coronary artery disease (CAD). Studies on the relationship between Environmental endocrine disruptors (EEDs) like BPA exposure as a risk factor for CAD have just lately come to light**.** Aim**:** The goal of this work is to study the correlation between BPA exposure and angiographically graded coronary artery diseases. Methodology**:** 131 patients with coronary artery disease (CAD) and 131 controls, in the period from June 2021 to June 2022 were involved. Each and every participant underwent the following: Full medical history taking, questionnaire for lifestyle, Lipid profile**,** urinary BPA level estimation as well as Electrocardiogram, Echocardiography and Coronary angiography. Result**:** Urinary BPA concentrations in cases with incident CAD (mean value,1.80 µg/L) is higher than in control group (mean value 1.29 µg/L). The mean of BPA in patients with high grade severity of CAD (the highest Syntax score) was 2.025 ± 0.455, patients with low Syntax score had low mean of BPA level (1.510±0.689 µg/L). Conlusion**:** depending on the present results, it can be concluded that urinary BPA is positively correlated to Syntax score of CAD (angiographically graded coronary atherosclerosis) in a concentration dependent manner.

Keywords: bisphenol A, cardiovascular diseases, coronary artery diseases, endocrine disruption ,blood lipids.

Full length article **Corresponding Author*, e-mail: *nadatoxo89@gmail.com*.

1. Introduction

High-volume industrial chemical bisphenol A (BPA) is a component of epoxy resins and polycarbonate plastic (PC). Over 100 tonnes of BPA are emitted into the environment each year, out of a total annual production of over 3.5 million tonnes [1]. Primarily, it was used as an antioxidant supplement in the manufacturing of polyvinyl chloride (PVC) polymers in addition to being an initiator for the creation of the flame retardant tetrabromobisphenol A. The American Society of the Plastics Industry created the Resin Identification Coding system for plastics in 1988. It categorises plastics into seven kinds, each of which has a resin number from 1 to 7 [2]. The safest plastic recycling options are 2, 4, and 5, but plastic recycling options 1, 3, 6, and 7 must be avoided. The two main end products of the monomer BPA are polycarbonate and epoxy resins (70 and 20 percent, respectively) [3]. Currently, materials meant to come into contact with food, such as goblets, feeding bottles, microwave ovenware, re-usable plastic bottles, cups, plates, and microwave ovenware, are made of polycarbonate, while beverage cans and the internal coating of food are made of epoxy resins. BPA exposure might come from a variety of difficult-to-identify sources [4]. A multisource exposure from the most pertinent products and aggregated exposure routes should be used to estimate the total exposure. The source of exposure can be classified into food and non-exposure sources. Food exposure source included tap and mineral water, food contact materials, and

breast milk while non-food source included trans-dermal, trans-placental, air and dust, and occupational exposure also it through dental materials, medical devices, and thermal paper [5]. The human circulation carries the bisphenol A conjugates created in the liver to the kidney, where they are further eliminated in urine with a terminal half-life of below six hours [6]. Because ingested BPA is virtually completely eliminated from urine in 24 hours, BPA exposure can be estimated from urine levels. The BPA excretion rate per day in ng/day, which is considered to be equivalent to the daily intake, is calculated by multiplying the urine concentration of total BPA (ng/ml) by the 24-hour urinary output (ml) [7]. Different mechanisms can be used by bisphenol A to work, androgen receptors (ARs), thyroid hormone receptors (TRs), glucocorticoid receptors (GRs), and aryl hydrocarbon receptors (AhRs) are just a few of the body receptors that BPA can interact with. Epigenetic gene regulation and the production of oxidative stress are other proposed methods [8]. Approximately 12 million people die each year due to Coronary artery disease (CAD) [9], CAD usually referred to as coronary heart disease, has multiple underlying causes. Coronary artery diseases are any conditions or illnesses that affect the heart's blood vessels and circulation. Prior to the discovery of atherosclerosis, coronary artery disorders were thought to be a disease of cholesterol storage. To put it another way, CAD is an inflammatory atherosclerotic disease [10]. Acute myocardial infarction (AMI), unstable angina (UA), chronic stable angina pectoris (CSAP), ischemic cardiomyopathy, and even sudden death are all different types of CAD.

The risk factors for CAD are numerous and include smoking, high blood pressure, hyperuricemia, diabetes, hyperlipidemia and gychological stress from job strain. Those who have the hereditary condition homocystinuria are more likely to experience the early development of cardiovascular illnesses [11]. Any individual suspected of having coronary artery disease should do group of tests, including baseline electrocardiography (ECG), exercise radioisotope tests, echocardiography, coronary angiography, intravascular ultrasonography, and magnetic resonance imaging. Blood tests, such as those for cholesterol, high-sensitivity C-reactive protein, plasma ceramides, natriuretic peptides, and lipoprotein (a), can provide a wealth of information regarding the health of the heart. For instance, high blood levels of low-density lipoprotein (LDL) cholesterol may indicate an elevated risk of heart attack. The heart's size and form, as well as the contour of the big blood veins in the lungs and chest, are visible on the x-rays. anomalies such as calcium deposits within blood arteries and aberrant cardiac size or shape can be observed [12]. Research on environmental endocrine disruptors (EEDs) like BPA has increased over the past ten years as well as studies on the relation between EED exposure and the risk of CVD have just lately come to light [13]. Due to high incidence of CVD nowdays, It is required to investigate enviromental BPA exposure as an important risk factor [14]. So, the purpose of this work is to study the correlation between urinary BPA and angiographically graded CAD. The present study was carried out in the period from June 2021 to June 2022, in Forensic Medicine and Clinical Toxicology and Cardiovascular Departments, Mansoura University, Faculty of Medicine.

2. Materials and Methods

2.1 Ethical approval

An ethical approval was taken from the Institutional Research Board (IRB) (MD.21.02.417.R1) before performance of the study. Oral informed consent were obtained from all participants.

2.2 Study Population

The number of cases with CAD in this study was 131 and 131 participants with coronary arteries that are normal as control group from cardiovascular department were incorporated into this research. The study population was restricted to those with body mass index (BMI) ranging from 19-30. Each and every participant underwent the following: full medical history taking, questionnaire for lifestyle to detect different sources of exposure to BPA. Questionnaire of ***Nomura et al,*** [15] after modification was used, urinary BPA level estimation (free and conjugated) and full clinical investigations including Electrocardiogram (ECG), Echocardiography (Echo), Coronary angiography and lipid profile (triglycerides **(**TG**)**, high-density lipoprotein (HDL), and cholesterol).

2.3 Exclusion criteria

Patients with body mass index more than30, patients who had previously a heart transplant, smokers and alcohol consumers,and patient with history of diabetes mellitus (DM) were excluded. For angiography (Metformin treatment raised the risk of lactic acidosis and worsening renal function following angiography, hence individuals with pre-existing renal impairment were not allowed to participate. Patients with abnormal renal function, patients treated with antiplatelet agents or other anticoagulants, patients who have experienced severe prior adverse responses to injections of iodinated contrast medi and patients with coagulopathy (especially INR > 2, a PTT ratio > 2, platelet count < 50,000 x 10–6)) were also excluded.

2.4 Determination of lipid profile

Serum lipid profile was assessed by automated clinical chemistry analyzer (Cobas C311) by photometric assay. After that, the low-density lipoprotein (LDL) was obtaining by the following calculation: LDL= total cholesterol-(HDL+TG/5).

2.5 Determination of urinary BPA level

2.5.1 Urine sampling

From each subject, five ml of the morning urine were collected in a sterile polypropylene cup, and stored as soon as possible in glass tubes in deep freeze at -20°C until analysis.

2.5.2 Preparation of Stock solution of standard solution:

Stock solution of standard solution in conc. of 100µg/ml was prepared then serial dilutions were made to obtain conc. of (100, 80,60,40,20 and 10 ng/ml) filtered then 100 µl were injected in HPLC. This step was done at NAWAH lab.

2.5.3 Digestion of urine samples

For each 500 µL urine sample, 30 µL of 2M sodium acetate buffer (pH 5) was added, and then enzymatic hydrolysis was done by adding (20 µL) β-Glucuronidase

enzyme and placed in the incubator for16 hours at 37°C from 4 PM to 8 AM. Following hydrolysis, 100 µL of 2N HCL was added, and 5 ml of ethyl acetate was used to extract the hydrolysate then centrifugation was done. Thereafter, 4 ml of the supernatant layer was filtered by filter paper to a new tube then evaporated, and then the rest was re-constituted with 1 ml of potassium phosphate monobasic buffer solution, before injecting onto HPLC system. Sample was filtered then 100 µl were injected. All samples were injected in waters 2690 Alliance HPLC system equipped with a Waters 996 photodiode array detector.

2.5.4 HPLC analysis conditions

Column C18 Inertsil: 4.6x250mm, 5µm. Mobile phase: Phosphate buffer pH=3: Acetonitrile. (50%:50%)**.** Mode of elution: Isocratic**.** Flow rate: 1ml/min**.** Temperature: Ambient**.** Wavelength: 220 nm.

2.5.5 Adjustment to urinary creatinine concentration

BPA concentration (µg/L) was adjusted to the urinary creatinine concentration (mg/dl) which was measured using enzymatic method on automatic chemical analyzer to correct the urine volume. This was done by multiplying 100 by the volume-based (unadjusted) urinary BPA concentration (µg/L), then dividing the result by urinary creatinine concentration (mg/dl) and lastly the resulting adjusted urinary BPA level was expressed as (µg/L) [16]**.**

2.6 Statistical analysis

After revision, coding, tabulation, and introduction to a PC, the results obtained were processed using the Statistical Package for Social Science (IBM Corp., Released 2017). Armonk, NY: IBM Corp.; IBM SPSS Statistics for Windows, Version 25.0. The following data were provided, and appropriate analysis was carried out based on the kind of data collected for each parameter: Data normalcy: As a test of normalcy, the Kolmogorov-Smirnov test was employed, if the significance level is greater than 0.05, then normality is assumed. Descriptive statistics: parametric numerical data were represented by mean ± standard deviation (SD), while non-parametric numerical data were represented by median and range. For non-numerical data, frequency and percentage were employed. Analytical statistics: The statistical significance of the difference between two separate research groups using parametric data was evaluated using the Student T Test. The statistical significance of the difference between two separate study groups with non-parametric data was evaluated using the Mann Whitney Test (U test). To compare two or more groups, use the Chi-Square test. When more than 25% of cells have a count of fewer than five in tables (>2*2), the Monte Carlo test is used as a correction for the Chi-Square test. Regression analysis: both univariate and multivariate, had been used to determine whether dependent and independent risk factors of a categorical outcome were present. Level of significance: The results of significance tests are expressed as two-tailed probability. The degree of significance for each of the aforementioned tests was determined and reported as the likelihood of (p-value), with the following explanation of the findings: insignificant if the p-value is > 0.05. If the p-value is < 0.05, it is considered significant. Significant if the p-value is < 0.001.

3. Results

The statistical findings of the sociodemographic data of the groups under study are shown in Table 1. According to age in the case and control groups, respective mean ages were 60.60 ±7.02 y and 55.97 ± 6.83 y, besides there was a statistically significant difference between the both two groups under study (p < 0.001). The studied groups did not differ in terms of sex or BMI or residence or educational level in a statistically significant way. Regarding dyslipidaemia, there was a statistically significant difference between the tested groups (P < 0.001). Concerning HTN, HCV, and family history of CAD, no statistically significant variation was found between the analysed groups. The most prevalent comorbidity in the case group was dyslipidaemia accounted for 59.5%, and the least prevalent was the family history of CAD (16.8%). On the other hand, HCV was the predominant comorbidity in the control group accounted for 45.8% as shown in figure 1. No statistically significant difference was seen between the two studied groups as regard the sources of exposure to BPA used in the form of bottles made from plastic, microwave meals, restaurant food, and plastic dishes (P=0.629, 0.537, 0.694, and 0.207, respectively). On the other hand, there was a statistical significance as regard exposure to BPA from canned food eating such as (canned beans, canned fish or seafood, canned vegetables, canned juce or drinks) (table, 2).The urinary BPA concentration (µg/L) was accustomed to the concentration of creatinine in urine (mg/dl). Between the studied groups, urinary BPA concentrations in cases with incident CAD (1.80 ± 0.70 µg/L) was higher than that of control group (1.29 ± 0.67 µg/L), there was a statistically significant difference (P < 0.001) as presented in figure (2). Moreover, the extent of CAD was correlated to urinary BPA level. In patients with three vessels affected (n= 35), BPA level was 1.968 ± 0.652 µg/L. While in patients with two vessels (n= 61), it was 1.801± 0.718 µg/L in addition 1.695 ± 0.704 µg/L in patients with single vessel affected (n= 35) as shown in figure (3). The results of the electrocardiography parameters in the two studied groups is shown in Table 3. Regarding PR interval, P-wave duration, QRS duration, and QT mean interval, there were statistically significant differences between the studied groups (P < 0.001). Significant statistical differences were observed between both studied groups when the following echocardiographic parameters were analyzed: Left atrium diameter (LAD), inter-ventricular septum thickness (IVS), end-diastolic diameter (EDD), end-systolic diameter (ESD), end-systolic volume (ESV), and ejection fraction (EF) (P = 0.001, 0.005, 0.017, 0.011, 0.037, and 0.006, respectively) as shown in Table 4.

Table (5) displayed the following information based on the coronary angiography findings in cases with incident coronary artery disease: 13.7% of cases (n=18) had an obstructive lesion in the left main coronary artery (LMCA). Most cases of normality in the right coronary artery (RCA) and left main coronary artery (LMCA) were found to be respectively 70.2% (n=92) and 59.5% (n=78). On the other hand, obstructive lesions in the left anterior

descending (LAD) artery were present in 89.3% of cases (n=117). The left circumflex (LCX) artery had an obstructive lesion in 22.9% (n=30) of the cases, and a non-obstructive lesion in 39.7% (n=52) of the cases. The average number of impacted segments was 3.74 ± 1.79. According to the number of afflicted vessels, 46.6% of patients (n=61) had two or more affected vessels, whereas 26.7% of cases (n=35) had one or three damaged vessels. Syntax (a visual estimate of CAD burden and complexity) had a mean of 13.30 ± 8.48. Complex lesions such as bifurcations, chronic complete occlusions, thrombus, calcification, and tiny diffuse disease are taken into consideration by the SYNTAX score. The score for lesions with extremely complex coronary architecture goes from 0 to more than 60. The correlation between the mean of BPA and Syntax score in cases with incident coronary artery disease has a mean of 2.025 ± 0.455 BPA in patients with the highest Syntax score. Patients with low Syntax score had low BPA level (1.510±0.689 µg/L) as shown in table 6. The optimum cut off value for detecting CAD cases from controls in urine was > 1.155, which had 74% sensitivity and 58.6% specificity as shown in table 7 and Figure 4.

4. Discussion

The development and progress of cardiovascular diseases (CVD) are associated with exposure to the environmental factors, a nationwide survey of 6733 adults in Egypt revealed an overall prevalence of CAD of 8.3% [17]. The studies of environmental endocrine disruptors (EEDs) were increased in the last few years; however studies examining the relationship between EED exposure and the risk of CVD have only recently begun [18]. According to Fu et al. 2020 , BPA in plastic items is linked to human CVD [19]. Studying the relationship between urinary BPA level and angiographically graded coronary atherosclerosis is the goal of the current study. The 262 participants in the current study were divided into 131 control participants with no diseases in coronaries and 131 cases with CAD recruited from the Cardiovascular department. The age distribution of the case and control groups in our work revealed a statistically significant variation between both studied groups. The fact that many heart disease patients are elderly may help to explain this [20]. In this study, there were approximately twice as many male patients with CAD as female ones, it is well known that men have higher risk for CAD than women [21].On the other side, Persons over 50 have a higher CAD frequency than younger persons. Compared to men, women had a higher percentage of CAD (8.9% vs. 8%) [17]. Participants from urban areas were more likely to have CAD than from rural areas. Meanwhile Krishnan et al. (2016), stated that the prevalence of CAD does not differ between rural and urban areas in Kerala, South India [22]. In an additional study, the incidence of CAD augmented from 1.4% in 1993 to 4.0% in 2009 in rural areas, and from 3.2% in 1990 to 12.6% in urban settings [23]. According to previously published reports, the probability of CAD and coronary risk factors is two or three times higher in metropolitan regions than in rural ones due to a higher rate of sedentary behaviour and alcohol consumption [24]. The comorbidities that were prevalent in the two studied groups included dyslipidemia, hypertension, hepatitis C virus (HCV), and a family history of CAD. While in the study done by Krishnan et al. (2016), the risk factors were being physically inactive 17.5%, also 18% reported having a family member with CAD. Other identified risk factors for CAD are abdominal obesity (57%), being overweight or obese (59%), high total cholesterol (52%), hypertension (28%), low levels of HDL cholesterol (39%) [22]. According to HTN, HCV, and family history of CAD, between the tested groups, there had been no statistically significant variation.. Regarding dyslipidemia, there was a statistically significant difference between the tested groups. The most prevalent comorbidity in the case group was dyslipidemia but HCV was the most prevalent in the control group, perhaps because of HCV infection is a major public health burden in Egypt. To determine BPA levels in urine for the current investigation, creatinine content must be taken into account. Data from the National Health and Nutrition Examination Survey (NHANES) showed that diuresis had no effect on the urine creatinine used as a reference analyte. Participants with highly concentrated urine samples would have their BPA levels overestimated, while respondents with diluted samples would have their BPA levels underestimated without accounting for urine concentration [25]. There was statistically significant variation between the studied groups concerning urinary BPA level; the mean of BPA level is higher in case group. This outcome is consistent with Melzer et al., (2012) where patients with normal coronary arteries had a median (unadjusted) uBPA value of 1.28 ng/mL, whereas patients with severe disease had a median uBPA value of 1.53 ng/mL [26].

In our study, the reported sources of BPA exposure were consuming plastic bottles, microwave meals, restaurant food, and plastic dishes, regarding these sources, there was no statistically significant difference between the two tested groups. However, a statistically significant difference was seen between the groups under investigation when it came to exposure to BPA from eating canned food. This could be explained by the modernization in the last years and the availability of different plastic tools and food packaging materials coated interiorly by BPA. The most common source of exposure to BPA was using plastic bottles in the two tested groups without significant difference between them. Plastic bottles are well known significant source of BPA exposure [27]. The small sample size may explain the non-significant difference between the two groups. According to the relationship between the mean BPA level and the number of diseased vessels, the mean BPA level was highst in cases with three damaged vessels and least in cases with single vessel affection. Regarding the relation between the mean BPA level and the CAD severity score (Syntax score), in patients with more severe CAD (highest Syntax score), the mean BPA was the highest. This finding means that there was positive correlation between BPA level and severity of CAD. These findings emphasize previous results which concluded that the diagnosis of coronary artery disease was substantially correlated with increased urine BPA values [28] and greater urine concentrations of BPA, are consistently linked to reported heart disease in adult population of the USA [29]. In another study done by Melzer et al.,Melzer et al., (2012) [26], in the group with three vessels of coronary artery stenosis, the mean concentration of bisphenol A was 3.82–6.31 ng/mL, compared to 2.13–2.73 ng/mL in the normal group. It was suggested that BPA could increase pro-

inflammatory gene expressions for CRP secretion increasing risk of CVD symptoms [14]. There are another possible mechanisms for explanation of correlation between BPA exposure and CVD.

Table 1: Socio-demographic Characteristics of Cases (with incident coronary artery disease) and Controls (n=262).

	Control group (n= 131)	Cases group (n= 131)	Test of significance	P value
Age (Years)	55.97 ± 6.83	60.60 ± 7.02	t= -5.406	< 0.001*
BMI (Kg/m^2)	24.16 ± 3.32	24.38 ± 3.28	t= -0.563	0.574
Sex				
Males	74 (56.5%)	84 (64.1%)	$\chi2$ = 1.549	0.207
Females	57 (43.5%)	47 (35.9%)		
Educational level				
Illiterate/primary level of education	35 (26.7%)	25 (19.1%)	$\chi2$ = 3.240	0.198
Secondary	51 (38.9%)	64 (48.9%)		
University or higher	45 (34.4%)	42 (32.1%)		
Residence				
Urban	72 (55%)	74 (56.5%)	$\chi2$ = 0.062	0.804
Rural	59 (45%)	57 (43.5%)		

Quantitative data expressed as mean ± SD/Categorical data expressed as Number (%). $\chi2$: Chi-square test. t: Independent samples t-test. *: significant value < 0.05. P: probability. BMI: body mass index. Kg: kilogram, m: meter, n: number.

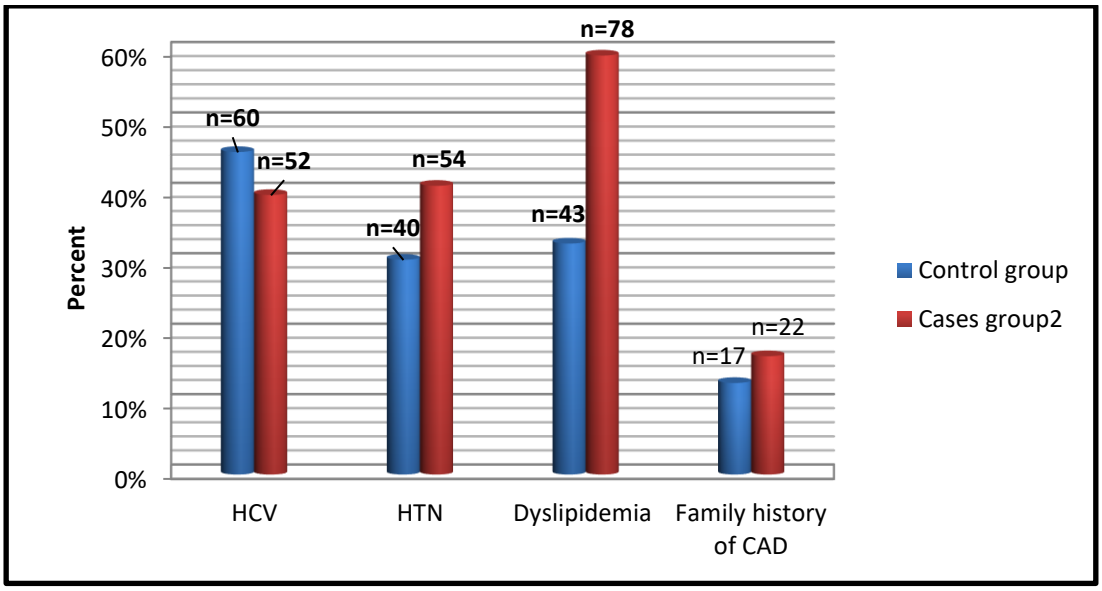

Figure 1: Comorbidities in the two studied groups included hepatitis c virus (HCV), hypertension (HTN), dyslipidaemia and family history of CAD. Categorical data expressed as (%) percentage and numerical (n).

Table 2: Comparison of the sources of bisphenol exposure in the two study groups (n:262)

	Control group (n= 131)	Cases group (n= 131)	Test of significance	P value
Canned food	46 (35.1%)	71 (54.2%)	$\chi2$= 9.952	0.002*
Plastic bottles	109 (83.2%)	106 (80.9%)	$\chi2$= 0.233	0.629
Microwave meals	63 (48.1%)	68 (51.9%)	$\chi2$= 0.382	0.537
Restaurant food	45 (34.4%)	42 (32.1%)	$\chi2$= 0.155	0.694
Plastic dishes	92 (70.2%)	101 (77.1%)	$\chi2$= 1.594	0.207

Categorical data expressed as Number (%), χ2: Chi-square test. P: probability.*: significant value < 0.05.

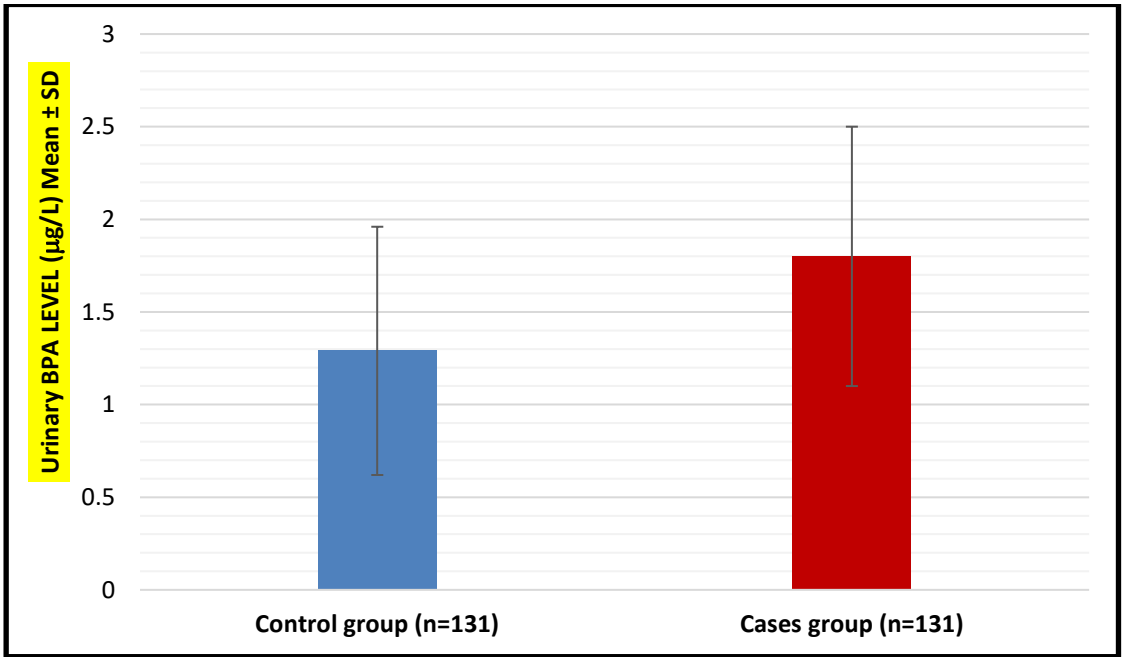

Figure 2: Urinary BPA levels in the two studied groups.

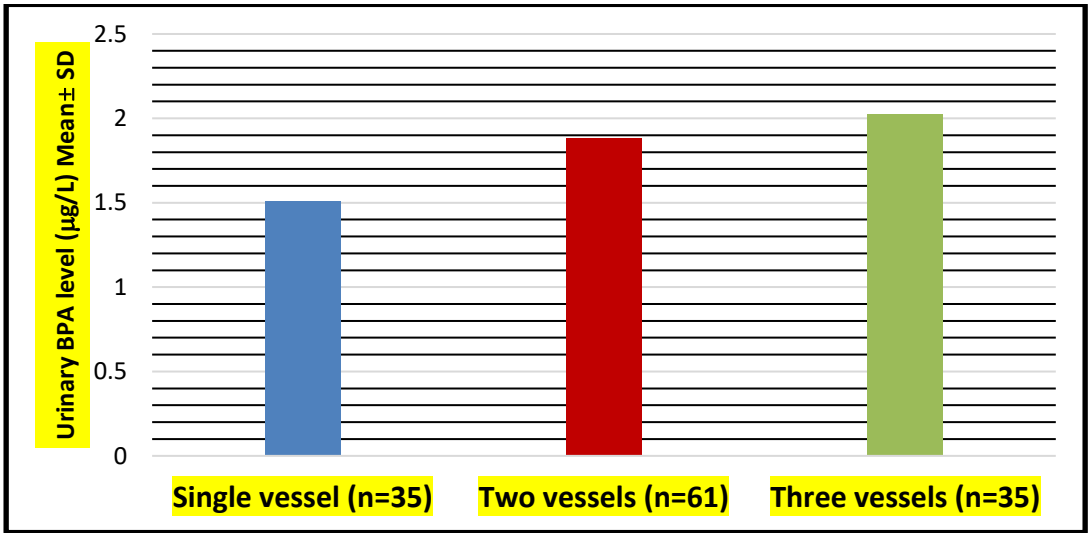

Figure 3: Urinary BPA levels according to the extent of CAD (number of vessels affected) in cases with incident CAD (number =131).

Table 3: Comparison of the electrocardiography parameters in the two studied groups (n:262)

	Control group (n= 131)	Cases group (n= 131)	Test of significance	P value
Resting heart rate (beats/min)	78.99 ± 11.61	76.79 ± 12.39	t= 1.488	0.138
P-wave duration (ms)	110.94 ± 7.02	107.78 ± 8.02	t= 3.394	0.001*
PR interval (ms)	113.89 ± 6.72	118.20 ± 10.45	t= - 3.973	< 0.001*
QRS duration (ms)	96.66 ± 14.02	90.96 ± 8.23	t= 4.014	< 0.001*
QT mean interval (ms)	449.36 ± 14.03	419.08 ± 45.63	t= 7.260	< 0.001*

Quantitative data expressed as mean ± SD, P: probability. t: Independent samples t-test, *: significant value < 0.05. (ms): millisecond, min: minute.

Table 4: Comparison of the echocardiographic parameters in the two studied groups (n:262)

	Control group (n= 131)	Cases group (n= 131)	Test of significance	P value
LA d	35.76 ± 5.07	38.78 ± 5.69	t= -4.539	< 0.001*
IVS	1.37 ± 0.21	1.46 ± 0.30	t= -2.822	0.005*
PWT	1.43 ± 1.48	1.24 ± 0.24	t= 1.418	0.157
EDD	5.37 ± 0.53	5.51 ± 0.45	t= -2.398	0.017*
ESD	3.74 ± 0.69	3.95 ± 0.60	t= -2.574	0.011*
EDV	143.13 ± 33.33	149.96 ± 28.12	t= -1.791	0.074
ESV	64.09 ± 30.06	71.35 ± 25.82	z = -2.097	0.037*
EF	56.48 ± 10.29	52.98 ± 10.09	t= 2.777	0.006*

Quantitative data expressed as mean ± SD. P: probability. z: Mann-Whitney U-test/ t: Independent samples t-test. *: significant value < 0.05. IVS: inter-ventricular septum thickness, LAD: Left atrium diameter. EF: ejection fraction, EDV: end-diastolic volume, ESV: end-systolic volume, EDD: end-diastolic diameter, ESD: end-systolic diameter, PWT: Posterior wall thickness .

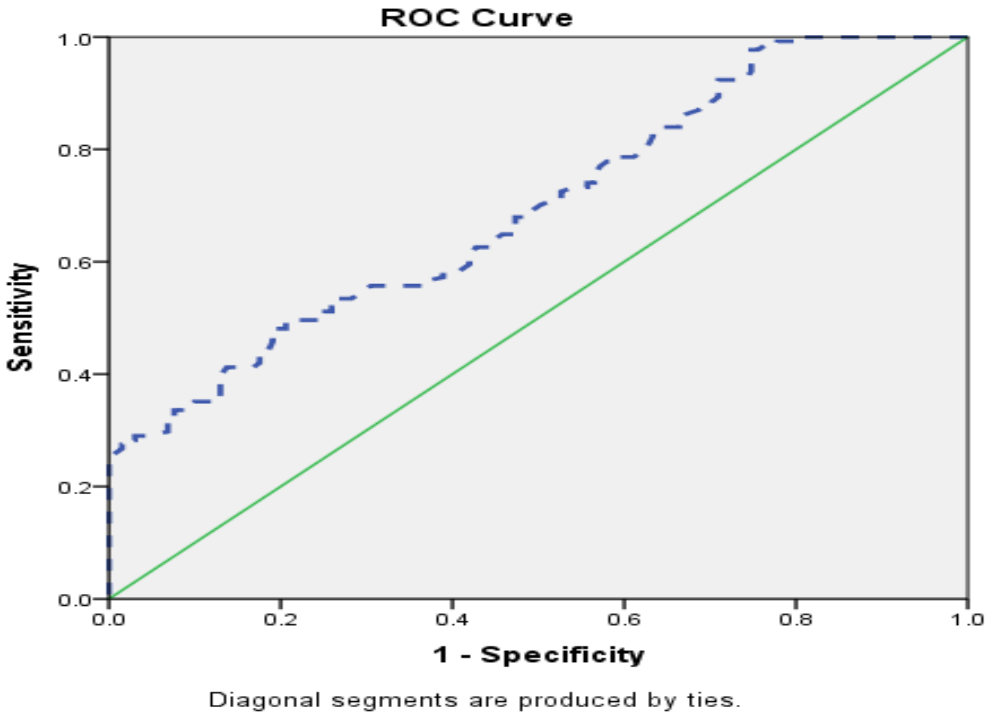

Figure 4: Differentiation between Group 1 and Group 2 by urinary BPA levels.

Table 5: Results of angiography in the Cases (With Incident Coronary Artery Disease) (n:131)

	Cases group = 131	
	Number	**Percent (%)**
The left main coronary artery (LMCA)		
Normal	92	70.2
Non-obstructive lesion	21	16.0
Obstructive lesion	18	13.7
Left anterior descending coronary artery (LAD)		
Normal	6	4.6
Non-obstructive lesion	8	6.1
Obstructive lesion	117	89.3
left circumflex artery (LCX)		
Normal	49	37.4
Non-obstructive lesion	52	39.7
Obstructive lesion	30	22.9
The right coronary artery (RCA)		
Normal	78	59.5
Non-obstructive lesion	37	28.2
Obstructive lesion	16	12.2
Number of affected segments	3.74 ± 1.79 (0-8)	
Number of vessels		
Single vessel	35	26.7
Two vessels	61	46.6
Three vessels	35	26.7
SYNTAX score	13.30 ± 8.48 (3-49)	

Categorical data expressed as Number (%), Quantitative data expressed as [mean ± SD (min-max)].

Table 6: Comparison of BPA level according to the severity of CAD (Syntax score)

CAD cases	**Low Syntax score (0-22)**	**Intermediate score (23-33)**	**High Syntax score (> 33)**	**Test of significance**
(n= 131)	**(n= 72)**	**(n= 36)**	**(n= 23)**	
BPA level (µg/L)	**1.510 ± 0.689**	**1.884 ± 0.705**	**2.025 ± 0.455**	**KW = 2.174 P= 0.112**

Table 7: Predictive value of urinary BPA to differentiate between Cases group with CAD and Control.

	Urinary BPA level
AUC	0.695
Cut off point	**> 1.155**
Sensitivity	**74%**
Specificity	**58.6%**
PPV	**78.2%**
NPV	**64.2%**
Accuracy	**68.3%**
P	< 0.001*

AUC: Area under curve, PPV: positive predictive value, NPV: Negative predictive value.

It has been observed that BPA inhibits the cardio-protective actions of 17β-oestradiol on isolated hearts of guinea pig that injured by ischemia. Moreover, 17β-estradiol may exacerbate symptoms particular to women caused by BPA, such as arrhythmia [30]. It has been documented that BPA functions as an agonist for the G-protein estrogen receptor (GPER), membrane ERs, and nuclear estrogen receptors ERα and ERβ. Recent research employing an estrogen responsive-TG zebrafish model has directly demonstrated which documented detrimental cardiac toxicities resulting from BPA exposure in animals may be mediated by ER signaling [31]. BPA exposure targets several biological pathways, such as 1) nuclear receptor and calcium signaling, 2) lipid metabolism and 3) extracellular matrix (ECM) interactions, which are essential in regulating heart function and development, according to cardiac transcriptome research [32]. Low concentrations of BPA have been shown to inhibit the synthesis of nitric oxide (NO) in cardiomyoblasts and to increase lipid peroxidation, oxidative stress and proinflammatory interleukin production [33].

5. Conclusion

According to the results of this study, BPA levels are higher in CAD patients than in the control group and there was positive correlation between BPA level and severity of CAD.

Limitation of study

This study has certain limitations because of its limited sample size and single center design. Larger studies are needed to estimate true response relationships and to detect different mechanisms underlying this connection.

Sources of Funding

None.

Authors' contributions

Nada El badrawy and sahar Eldakroory designed the study and established the model of the study. Ahmed Ibrahim Bedier examined the patients and performed the cardiac examination. Data collection and analysis were performed by Nada El badrawy, Eman Abdelrazik and Amal EL-Bakary. All authors wrote, revised the manuscript, and approved the final manuscript.

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