The possible association between Bisphenol A exposure and type 2 Diabetes Mellitus

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Abstract

Background: Diabetes is becoming more widespread over the world. Egypt is among the top ten countries in the world in the number of diabetes patients according to the International Diabetes Federation. Bisphenol A is widely used in the production of polycarbonate plastics, epoxy resins, food and beverage containers. Bisphenol A is a metabolic disruptor in addition to an endocrine disruptor. **Purpose:** This study aims to evaluate the possible association between bisphenol A and type 2 Diabetes Mellitus among Egyptian samples.

Methods: We collected urine samples from (100) adult participants dividing into two major groups, cases group consisted of 50 patients with type 2 DM and control group consisted of 50 normal adult persons. Subjects in the cases group were selected from the attendants of the Diabetes Endocrine & Metabolism outpatient clinic, Kasr-Alainy, Cairo University hospitals. In urine, bisphenol A was measured using high-performance liquid chromatography (HPLC).

Results: Regarding bisphenol A levels among the studied groups, there was a highly significant statistical difference between the cases and the control group with p value<0.001. The mean body mass index was 27.32 ± 3.32 for cases and 25.02 ± 1.87 for the control group with p value<0.001.

Conclusion: The current study found that type 2 DM was associated with high levels of bisphenol A metabolites in urine.

Keywords: (Bisphenol A, Type 2 DM, Body Mass Index, Exposure).

INTRODUCTION

According to the definition of diabetes mellitus (DM), it is "a collection of metabolic diseases characterized by hyperglycemia due to abnormalities in insulin secretion, insulin action, or both. Hyperglycemia results from uncontrolled diabetes and leads to serious damage disease to many body systems especially nerves and blood vessels [1].

In early 2020, there were 8,850,400 adult diabetes patients in Egypt, with a prevalence of 15.2%, placing Egypt eighth in the world for DM prevalence. It is expected that the number of diabetic patients in Egypt will reach 13.1 million by 2035 [2].

Bisphenol A (BPA) was first synthesized by Dianin in 1891 who tested it as a synthetic estrogen in the early 1930s. It is a synthetic chemical that has been utilized in several industrial applications for more than 50 years, involving the production of epoxy resins, polycarbonate plastics, other polymers, and thermal sheet. worldwide consumption: was estimated at 7.7

million metric tonnes in 2015, with a sharp projection to 10.6 million tonnes in 2022 [3].

BPA accumulated in the surrounding environment and released from consumer items has the potential to reach the body through the oral route (ingestion of canned and food stored in plastic containers and drinking of polluted water), Transdermal absorption (through skin contact with thermal paper, medical equipment as nebulizers, and toys as dummies), Inhalation (dust containing BPA, vapors and, gases resulting from burning of plastics containing BPA) and Parenteral (via syringes, cannulas and IV lines) [4].

Canned food is the most common source of BPA. Food packing products containing epoxy resins are the most common source of BPA contamination in food. Internal can coatings, such as epoxy resins and polyvinyl chloride (PVC) organosols, are frequently used to avoid direct contact between the food or drink and the metal can walls, as well as to avoid rust and corrosion. BPA was found at significant concentrations in composite foods stored in cans, such as canned fish, which had the highest BPA level (106ng/g) [5].

BPA is a xeno-estrogen and an endocrine-disrupting substance that harms endocrine function. BPA is abundant in everyday life; hence human populations are constantly exposed to it. It has been linked to a variety of metabolic problems, most notably type 2 diabetes mellitus (DM) [6].

BPA disrupts the metabolism in addition to disrupting the endocrine system. It has been established that higher levels of inflammatory indicators (IL-6 and TNF-), receptor markers, and other markers are paralleled by exposure to BPA. Insulin resistance and poorer glycemic control are strongly linked with BPA concentrations. Patients with diabetes mellitus also have higher levels of estrogen-related receptor gamma (ERR), which was recently discovered to function as a BPA receptor [7].

BPA exposure can trigger changes in the β-cell life cycle, with increased apoptosis and decreased proliferation leading to a reduced β-cell mass resulting in a decrease in the mass of β-cells. The expression of some cell cycle inhibitors, such as cyclin-dependent kinase inhibitor 2A (CDKN2A), and some cell cycle activators, such as c-cycles D2 (CCND2), increased and decreased, respectively, are at least partially responsible for these effects [8]

Additionally, experimental studies have shown that BPA may impact insulin signalling in insulin-sensitive organs as well as insulin production and secretion in pancreatic beta-cells [9]. BPA causes a cascade of caspases to be activated when it potentiates the pro-apoptotic protein (Bax) and lowers the anti-apoptotic protein (Bcl-2). Pancreatic β-cells undergo apoptosis when activated caspases are present [10].

MATERIALS AND METHODS

Study design and population

It was a case-control study that was conducted during the period from November 2020 to May 2022 and included 100 adult participants including 50 patients with type 2 diabetes mellitus attending to Diabetes Endocrine and Metabolism outpatient clinic, Kasr-Alainy, Cairo University hospitals, and 50 normal adult persons. Informed consent was taken from all participants before the study. Kasr-Alainy Faculty of Medicine's Ethics Committee approved the study protocol (code: MD 335-2020).

Our study included adult patients above eighteen years old with type 2 DM and we excluded patients with type 1 DM, liver failure, renal failure, and malignancy.

Study measurements

Sociodemographic data, such as sex, age, work, residence, education, and social habits were collected. A questionnaire demonstrating the dietary, environmental, occupational, and medical

exposure to bisphenol A was also filled.

Their weights and heights were measured then the body mass index (BMI) was estimated by weight (kg)/height2 (m)2 (normal BMI=18 to <25, overweight =25 to <30, and obese ≥30 kg/m2).

Lipid profile was done.

Sample preparation

Urine samples were collected in clean glass containers from cases and control groups in the morning at 9: 00 am marked with coding number for each participant, whereas we excluded any turbid samples from the study. Refractometry was then used to determine the specific gravity to identify sample dilution. All samples were then kept at 20°C and analyzed by high-performance liquid chromatography (HPLC) to determine the mean levels of bisphenol A (BPA) (i.e., the mean value was determined using three different readings taken at different times).

Chemicals used

Bisphenol A (>97%) was obtained From Alfa Aesar, Bisphenol B was obtained from SIGMA-ALDRICH, Methanol, acetonitrile, and tetrahydrofuran were obtained from ADVENT CHEMBIO PVT.LTD, All solvents were HPLC grade. A direct-Q gradient 8 UV system was used to purify the water (Millipore).

Instruments and chromatographic conditions

A high-pressure isocratic system consisting of a Dionex UltiMate 3000 UHPLC; column, RS pump, compartment, autosampler, and fluorescent detector was used. Chromatographic column reversed phase 150mm× 4.6 mm Hypersil BDS, C18 particle size 5u. Data acquisition and interpretation were done using Chrome Leon 7 software.

500 μL of urine was buffered with 30 μL of 2.0 M sodium acetate buffer (pH 5) before hydrolysis by β-glucuronidase enzyme at 37 °C for three hours in a shaking water bath. A 100 μL (2N HCl) was added, and the hydrolysate was extracted once with 5 mL of ethyl acetate with 50 ng/ml bisphenol B (internal standard). After centrifugation, 4 ml supernatant was put to a new tube and then evaporated. 200 μL of 60% acetonitrile were used to dissolve the residue in water. 40 μL of sample was injected by autosampler into HPLC. Tetrahydrofuran, acetonitrile, and water were mixed (35:35:130 and, 70:35:95) in the gradient mode to prepare the mobile phase. The fluorescence detector used excitation and emission wavelengths of 275 and 300 nm respectively to detect samples.

Solid-phase extraction

Conditioning: Following the addition of 1 mL of acetonitrile, 1 mL of phosphate buffer solution (pH 2) and 1 mL of methanol were added.

Loading: Hydrolyzed urine sample (with 10 ul bisphenol B as internal standard) was diluted with 1 mL of phosphate buffer solution and then added to the SPE column.

Wash: The cartridges was washed by 2 mL formic acid solution (0.1 M) and 1 mL water. Then, the cartridges were dried under negative pressure.

Elution: 1 mL of ethyl acetate and 1 mL of acetonitrile were added. The eluent was collected, concentrated, and evaporated. 1 ml of mobile phase was used to reconstitute the dry residue.

Chromatographic conditions

Mobile phase:

• Mobile phase (1) acetic acid (0.1%) in water and mobile phase (2) acetic acid (0.1%) in HPLC grade acetonitrile.

• The setting of the column's temperature was at 40°C.

• 20 µL of the sample was injected, and the flow rate was 0.3 mL/min. UV was set from 240 to 280 nm maximum absorbance was 254 nm.

Statistical analysis

The statistical software for the social sciences (SPSS; version 26) was used to code and analyze the data (IBM Corp., Armonk, NY, USA). Quantitative data were represented using the mean, SD, median, minimum, and maximum, while frequency (count) and relative frequency (%) were used to summarize the categorical data. The Mann-Whitney tests and non-parametric Kruskal-Wallis were used to compare quantitative variables [11]. The Chi-squared test was used to compare categorical data. When the expected frequency was less than five, the exact test was utilized instead [12]. The Spearman correlation coefficient was employed to calculate the correlations between the quantitative variables [13]. p value less than five was considered statistically significant.

RESULTS

Clinical data

The basic clinical characteristics of the studied groups are shown in Table 1. Overall, there was no statistical difference between the studied groups regarding age, sex and residence, work, and smoking. while there was a significant difference regarding BMI and lipid profile.

Exposure

Table 2 shows a statistically significant differences between cases and control regarding the use of canned food, packaged food, cans, food stored in PVC containers, plastics, fast foods, dental materials, and medical devices. While it shows no statistical difference between the studied groups regarding the use of microwave meals and thermal papers.

Measurement of bisphenol A in urine

Table 3 and figure 1 show a statistically significant differences between cases and control regarding the level of BPA in urine.

Relation between bisphenol A and exposure data in the cases group

Table 4 shows a statistically significant differences between BPA and the use of Canned food, packaged food, Microwave meals, Cans, Food storage in PVC containers, plastics, fast food, thermal paper, dental materials, and medical devices.

Relation between bisphenol A and BMI and lipid profile in the cases group

Table 5 and figure 2 show a significant correlation between high BPA levels and increased BMI in the cases group. Figure 3 shows a significant correlation between high BPA levels and abnormal lipid profile.

Table 1: Clinical characteristics of studied groups.

Variables	Cases (n=50)	Control (n=50)	Test	P value

Age (mean ± SD)	48.40 ± 5.52	47.86 ± 5.48	t-test	0.625
Sex			(χ2) test	0.391
Females	36 (72%)	32 (64%)		
Males	14 (28%)	18 (36%)		
BMI (mean ± SD)	27.32 ± 3.32	25.02 ± 1.87	t-test	< 0.001*
BMI			(χ2) test	< 0.001*
Normal	20 (40%)	39 (78%)		
Overweight	18 (36%)	11 (22%)		
Obese	12 (24%)	0 (0%)		
Residence			(χ2) test	1
Urban	34 (68%)	34 (68%)		
Rural	16 (32%)	16 (32%)		
Work			(χ2) test	0.309
Yes	18 (64%)	23 (46%)		
No	32 (36%)	27 (54%)		
Smoking			(χ2) test	0.812
Yes	12 (24%)	11 (22%)		
No	38 (76%)	39 (78%)		
lipid profile			(χ2) test	< 0.001*
Normal	30 (60%)	46 (92%)		
Abnormal	20 (40%)	4 (8%)		

Table 2: Exposure of studied groups to BPA sources.

Exposure	Frequency	Cases (n=50)	Control (n=50)	Test ($\chi 2$) test	P value
Canned food	Rarely	0 (0%)	20 (40%)		< 0.001
	once / week	37 (74%)	28 (56%)		
	2-4 times/week	12 (24%)	2 (4%)		
	>4 times/week	1 (2%)	0 (0%)		
Packaged food	Daily	14 (28%)	2 (4%)		< 0.001
	Weekly	30 (60%)	19 (38%)		
	Rarely	6 (12%)	29 (58%)		
Microwave meals	No	40 (80%)	35 (70%)		0.248
	sometimes	10 (20%)	15 (30%)		
	Always	0 (0%)	0 (0%)		
Cans	Rarely	17 (34%)	38 (76%)		< 0.001
	once / week	24 (48%)	10 (20%)		
	2-4 times/ week	5 (10%)	2 (4%)		
	>4 times/week	4 (8%)	0 (0%)		
Food storage in PVC container	No	21 (42%)	38 (76%)		0.001
	sometimes	24 (48%)	12 (24%)		
	Always	5 (10%)	0 (0%)		
Plastics	Rarely	5 (10%)	0 (0) %		< 0.001
	once / week	22 (44%)	47 (94%)		
	2-4 times/ week	16 (32%)	3 (6%)		
	>4 times/week	7 (14%)	0 (0%)		
Fast food	Rarely	35 (70%)	23 (46%)		< 0.001
	1-2/ week	4 (8%)	19 (38%)		
	3 / week	5 (10%)	8 (16%)		
	>4 / week	6 (12%)	0 (0%)		
Thermal paper	Rarely	38 (76%)	45 (90%)		0.062
	Sometimes	12 (24%)	5 (10%)		
	Always	0 (0%)	0 (0%)		
Dental materials	No	36 (72%)	47 (94%)		0.003
	sometimes	14 (28%)	3 (6%)		
	Always	0 (0%)	0 (0%)		

Medical devices	Yes	24 (48%)	6 (12%)		< 0.001
	No	26 (52%)	44 (88%)		

Table 3: comparison between the cases and the control regarding urinary BPA levels.

	Cases (n=50)			Control (n=50)			Test	P value
	Median	1st quartile	3rd quartile	Median	1st quartile	3rd quartile		
BPA level (µg/ml)	1.14	0.75	3.56	0.37	0.21	0.59	nonparametric Mann-Whitney test	<0.001*

Table 4: the relation between BPA level and exposure data in the cases group.

		BPA level			Test	P value
		Median	1st quartile	3rd quartile	non-parametric Kruskal-Wallis test and Mann-Whitney test	
Canned food	once / week	0.89	0.73	1.38		< 0.001*
	2-4 times/ week	4.75	3.39	12.72		
	>4 times/ week	47.87	47.87	47.87		
Packaged food	Daily	5.71	3.36	10.76		< 0.001*
	Weekly	0.90	0.75	1.87		
	Rarely	0.57	0.54	1.82		
Microwave meals	No	0.95	0.74	2.12		< 0.001*
	sometimes	6.79	3.56	14.67		
Cans	Rarely	0.73	0.62	0.75		< 0.001*
	once / week	1.72	1.05	3.19		
	2-4 times/ week	5.50	4.00	8.41		
	>4 times /week	14.04	10.17	32.59		
Food storage in PVC container	No	0.75	0.64	1.05		< 0.001*
	sometimes	2.12	0.92	3.78		
	Always	14.67	10.76	17.31		
Plastics	Rarely	0.55	0.54	0.58		< 0.001*

	once / week	0.84	0.75	1.05	
	2-4 times/ week	2.92	1.84	3.78	
	>4 times/ week	14.67	9.57	19.16	
Fast food	Rarely	0.89	0.73	1.61	< 0.001*
	1-2/ week	4.43	3.02	6.96	
	3 / week	3.17	1.05	3.99	
	>4 / week	15.99	10.76	19.16	
Thermal paper	Rarely	0.94	0.73	1.87	< 0.001*
	Sometimes	7.74	3.58	15.99	
Dental materials	No	0.86	0.73	1.37	< 0.001*
	sometimes	5.71	3.36	14.67	
Medical devices	Yes	2.92	1.11	5.71	0.002*
	No	0.84	0.73	1.38	

Table 5: the relation between BPA level and BMI in the cases group.

	BPA level			
	Correlation Coefficient	Test	P value	N
BMI	0.778	Spearman correlation	<0.001	50

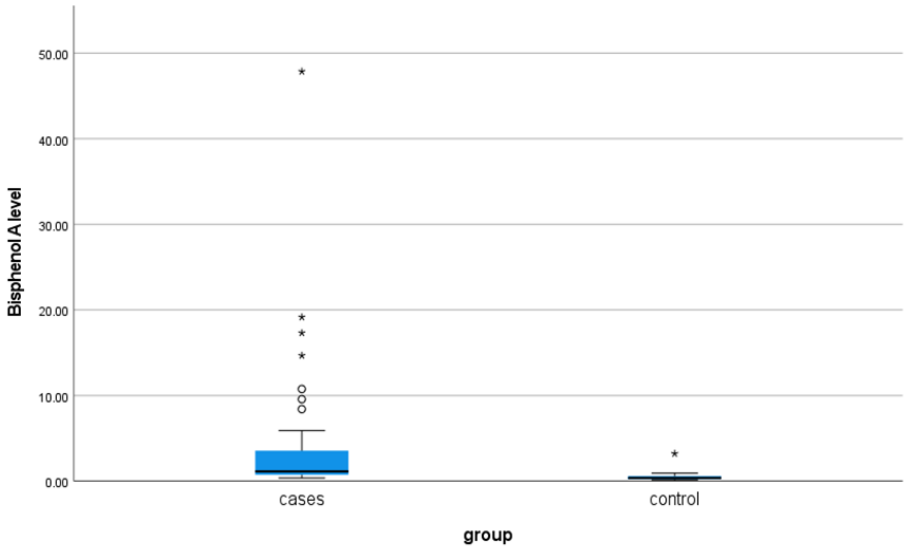

Figure 1: Box plot showing the comparison between the cases and the control groups regarding BPA level.

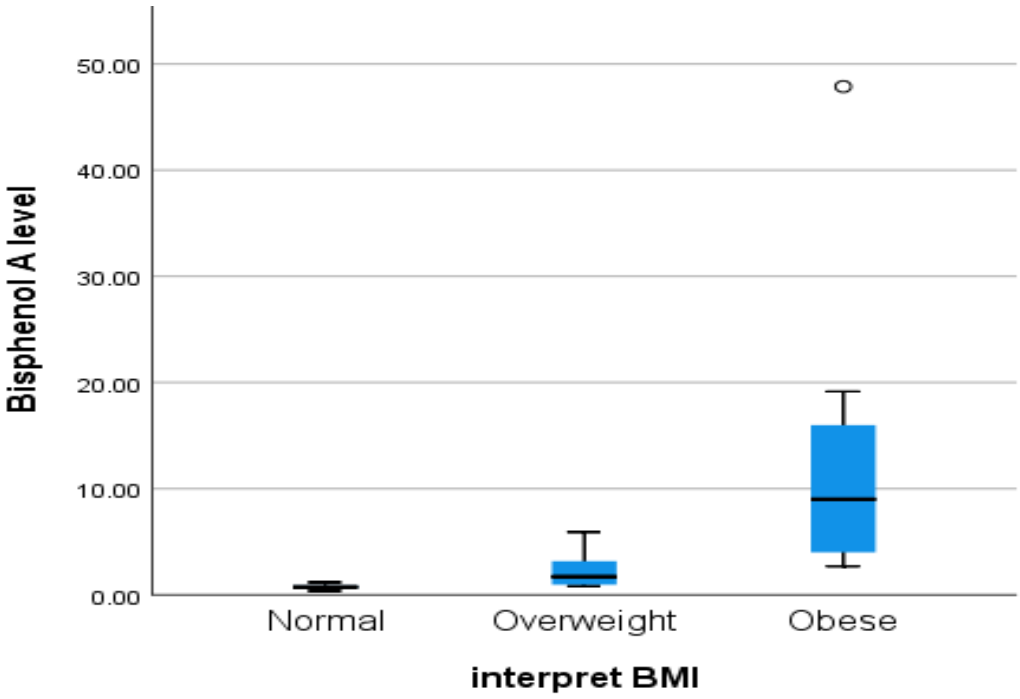

Figure 2: Box plot showing the relation between Bisphenol A level and BMI in cases group.

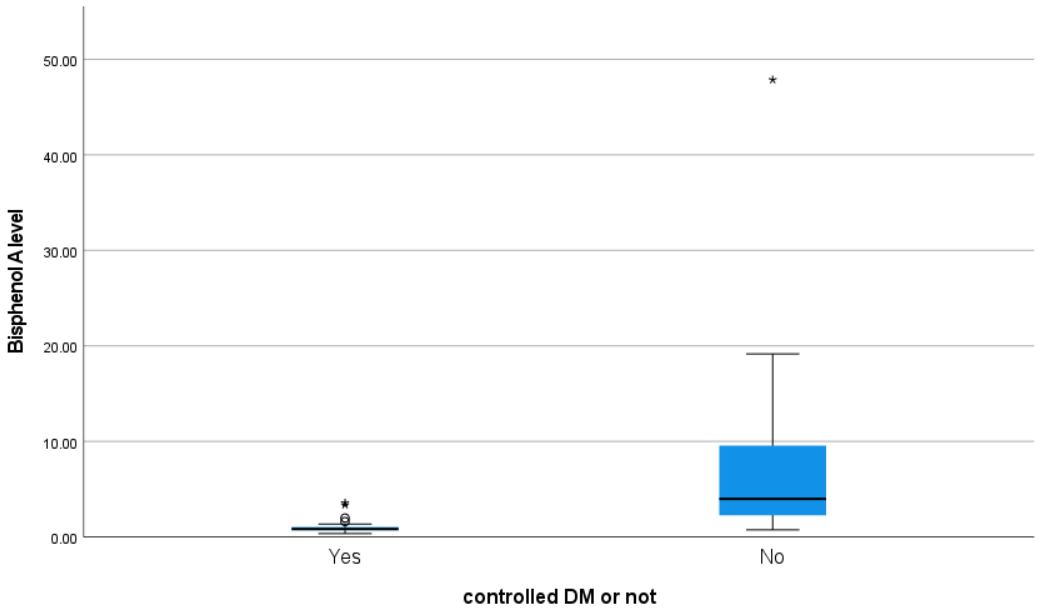

Figure 3: Box plot showing the relation between Bisphenol A level and the condition of DM (controlled or not).

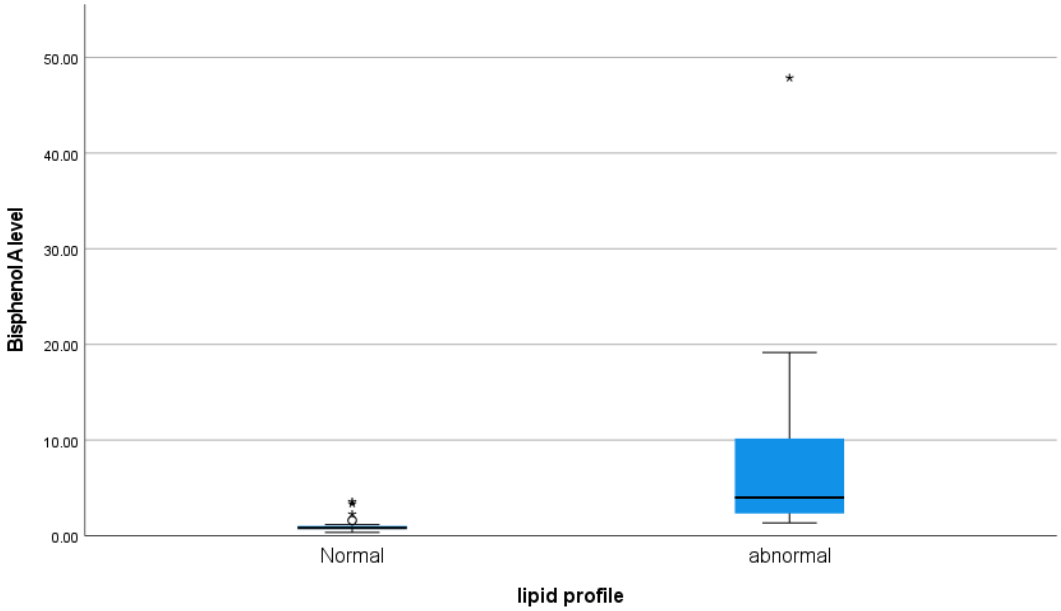

Figure 4: Box plot showing the relation between Bisphenol A level and lipid profile in cases group.

DISCUSSION

Regarding age distribution among the studied groups, the mean age was (48.40±5.52 years) for cases and (47.86 ± 5.48 years) for the control group with no significant difference between groups (p-value 0.625).

This contrasted with a study conducted by Ahmad khaniha et al., (2014) who reported that the mean age was (56.6 ± 9.7 years) for cases and (46.7 ± 8.5 years) for the control group with a significant difference between groups (p-value 0.001) [14].

Regarding sex distribution among the studied groups, there was no significant difference between the two studied groups (p-value 0.391) as the majority were females in both cases and control groups (72.0%, and 64.0% respectively). This was in accordance with (Ahmad khaniha et al., 2014) who reported that there was no significant difference between the two studied groups (p-value 0.332) as the majority were females in both cases and control groups (53.8%, and 60% respectively) [14].

Regarding the association between sex distribution and BPA level, there was no statistical difference between sex and BPA level among the cases group (p-value=0.12). This was in accordance with a study by Lehmler et al., (2018) who reported that there no was a statistical difference between BPA and sex (p-value 0.24) [3].

Regarding the relation between residence and BPA level, there was no statistical difference between residence and BPA level (p-value 0.540). This contrasted with a study by Tratnik et al., (2019) who reported that there was a statistically significant difference between residence and urinary BPA level (p-value 0.046) [15].

Regarding educational level among the studied groups, there was no significant difference between the two studied groups (p-value 0.936). This contrasted with a study by Salamanca-Fernández et al., (2020) who reported that there was a statistically significant difference between the two studied groups (p-value 0.028) [16].

Regarding the relation between educational level and BPA level, there was no significant

difference between them (p-value 0.053). This contrasted with a study by Bao, W et al (2020) in which a significant difference was found between educational level and BPA level (p-value 0.04) [17].

Regarding BMI among the studied groups, the mean BMI was (27.32±3.32kg/m2) for cases (group A) and (25.02±1.87 kg/m2) for controls (group B) with highly significant statistical difference between groups (A&B) (p-value < 0.001). This was consistent with a study conducted by Wang et al (2022) who reported that mean BMI was (25.7±3.33 kg/m2) for cases (group A) and (23.63±3.07 kg/m2) for controls (group B) with highly significant statistical difference between groups (A&B) (p-value < 0.0001) [18].

Regarding the relation between Bisphenol A and BMI among the cases group, a highly significant relation was found between BPA level and BMI in group A with (p-value < 0.001). This was consistent with a study conducted by Wang et al (2012) [19].

Regarding the association between BPA and type 2DM, there was a strong association between them among the studied groups with (p-value <0.001). This was in accordance with a study by Lang et al. (2008) that found a strong positive correlation between urine BPA concentrations and the prevalence of diabetes among 1,455 U.S. adults [20]

Several studies showed that due to decreased GLUT1 expression and insulin receptor phosphorylation, exposure to BPA seems to decrease adipocyte sensitivity to insulin. This suggests that BPA also causes abnormalities in glucose metabolism and raises the risk of developing type 2 diabetes [21].

Regarding the association between BPA level and lipid profile, there was a high statistically significant between lipid profile and Bisphenol A level with (p-value < 0.001). This agreed with the data of the United States National Health and Nutrition Examination Survey (NHANES) 2003–2008, Teppala et al., (2012) found a correlation between elevated BPA exposure and lipid profiles, including increased triglycerides and decreased high-density lipoprotein (HDL) levels [22]. Additionally, this was supported by Wang et al (2020) study which reported that elevated BPA concentrations were associated with higher levels of lipid profile among middle-aged and elderly Chinese adults [23].

LIST OF ABBREVIATIONS

BMI Body mass index

BPA Bisphenol A

DM Diabetes mellitus

HDL High-density lipoprotein

HPLC High performance liquid chromatography

NHANES United States National Health and Nutrition Examination Survey

References

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