Association between Bisphenol A exposure and dilated cardiomyopathy

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Abstract
Background: Evidence has identified bisphenol A to have detrimental environmental and health effects. There are few studies on the association between bisphenol A exposure and cardiovascular abnormalities including cardiomyopathies and cardiac arrhythmias.
Aim: Evaluation of the prevalence of bisphenol A exposure in patients with dilated cardiomyopathy versus healthy controls.
Methods: The study was a 1-year cross-sectional, single tertiary care cardiac centre, open-labeled, randomized, controlled study. Participants with dilated cardiomyopathy were included, while participants with ischemic cardiomyopathy were excluded. Eighty consecutive participants were selected and divided into 2 groups of 50 participants with dilated cardiomyopathy and 30 age and gender matched healthy participants and underwent transthoracic echocardiography.
Results: In the dilated cardiomyopathy group, bisphenol A was detected in 24% of the study participants, while in the healthy control group, bisphenol A was detected in 6.7%. There was a statistically significant weak association between bisphenol A exposure and dilated cardiomyopathy. In the dilated cardiomyopathy group, there was a statistically significant difference in the left atrial diameter and a highly significant difference in the tricuspid annular plane systolic excursion of the study participants exposed to bisphenol A versus not exposed to bisphenol A, and a highly significant strong association between bisphenol A exposure and right ventricular dilatation.
Conclusions: The prevalence of bisphenol A exposure was more in patients with dilated cardiomyopathy versus healthy controls and the volumetric indexes of the left atrial diameter and the right ventricular size and function were worse in patients with dilated cardiomyopathy exposed to bisphenol A versus patients with dilated cardiomyopathy not exposed to bisphenol A.

Keywords
Bisphenol A, Dilated cardiomyopathy, Echocardiography, Left atrium, Right ventricle

Introduction

Bisphenol A (BPA) is an industrial chemical used in the manufacturing of polycarbonate plastics for various consumer goods as food containers and epoxy resins for adhesives, paints, primers, and sealers[1]. Calafat et al. U.S. population-based study showed 92.6% prevalence of BPA exposure[2]. Observational studies on the adverse health effects of BPA have classified BPA as an endocrine disruptor and suggested association between BPA exposure and cardiovascular diseases including cardiomyopathies and cardiac arrhythmias[3,4]. Analysis of cross-sectional data collected by National Health and Nutrition Examination Survey 2003-2004 showed association between higher urinary BPA concentrations and reported angina, coronary artery disease (CAD), heart attack, diabetes mellitus (DM), and abnormal liver function[5]. As per the American Heart Association guidelines, dilated cardiomyopathy (DCM) is a group of genetic, environmental, or unknown disorders affecting the myocardium characterized by progressive ventricular dilatation and systolic dysfunction in absence of hypertension, valvular, congenital, or ischemic heart disease[6]. DCM has an estimated prevalence of 40 patients per 100,000 population[7]. Clinically, patients with DCM present with congestive heart failure (HF). In 2015, Xiong et al showed a highly significant difference in the serum BPA level of a cohort of DCM patients vs a cohort of healthy controls ($t(174) = 3.1$, $P = < 0.001$)[8]. There are few published studies which address the prevalence of BPA exposure and temporality of association in patients with DCM.

The study evaluated the prevalence of BPA exposure in patients with DCM versus healthy controls. Secondary objectives included assessment of the difference in the echocardiographic parameters of patients with DCM exposed to BPA versus patients with DCM not exposed to BPA.

Methods

1. Study design

Our study was a 1-year cross-sectional, single tertiary care cardiac centre, open-labeled, randomized, controlled study. The study design was approved by the hospital ethics committee and all participants signed written informed consents.

2. Study participants

Study participants were subjected to history taking and data collection for age, gender, risk factors including hypertension, DM, smoking and family history, comprehensive clinical examination,12 leads electrocardiogram (ECG) to detect ECG signs of left atrial (LA) abnormalities, CAD, and/or pulmonary hypertension (PH), two-

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dimensional, motion-mode and Doppler echocardiography using Siemens acuson-70® to measure LA, left ventricular (LV), and right ventricular (RV) size, assess LV and RV function, and screen for PH, and laboratory investigations including assessment of serum BPA level. Data documented with ECG include atrial fibrillation, left bundle branch block and right bundle branch block, while data documented with echocardiography include LA diameter, LV end diastolic diameter (LVEDD), LV end systolic diameter (LVESD), ejection fraction (EF), ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity, tricuspid annular plane systolic excursion (TAPSE), and pulmonary artery systolic pressure. Screened participants were excluded if they had ischemic cardiomyopathy, valvular or congenital heart diseases, thyroid, pituitary or adrenal disorders, end stage renal or hepatic failure, or received hormonal treatment.

3. Study procedures

Eighty eligible participants from in-and-out patients were randomly, consecutively assigned with an unequal allocation ratio into an open-labeled unblinded fashion. The enrolled study participants were divided into 2 groups of 50 participants with DCM and 30 age and gender matched asymptomatic participants with normal echocardiographic findings. In our study, we defined DCM by the symptoms of HF and the echocardiographic findings of dilated LV diameter (LVEDD of > 5.5 and LVESD of > 4.5) and impaired LV systolic function (EF of < 50%).

4. End points

The study evaluated the prevalence of BPA exposure in patients with DCM versus healthy controls. Secondary objectives included assessment of the difference in the echocardiographic parameters of patients with DCM exposed to BPA versus patients with DCM not exposed to BPA.

5. Statistical analysis

The echocardiographic assessment outcomes were coded, and the data was analysed with the Statistical Package for the Social Sciences software (SPSS®) version 25. Quantitative data was expressed as means and standard deviations, while qualitative data was expressed as medians and ranges. Comparisons between parametrically distributed quantitative variables were done with independent t-test, between non-parametrically distributed quantitative variables with Mann-Whitney test, and between qualitative variables with Chi-square test, respectively[9,10]. The confidence interval was set to 95% and the margin of error accepted was set to 5%. Any comparison considered statistically significant was at $P < 0.05$ or less and highly significant at $P < 0.01$. Final data analysis was as per Intention to treat analysis.

Results

1. Study participants and procedures

We recruited 80 patients from one centre in one country from 2015 through 2016. The two study groups were balanced with regards to baseline socio-demographic characteristics and risk factors (Table 1). The key sociodemographic feature of enrolled participants was male gender predominance (74% of DCM group and 76.7% of healthy control group were males). Age was not significantly different between both groups (mean age was 56.7 ± 12.8 years for DCM group vs 58.2 ± 9.8 years for healthy control group, $P = 0.568$). Risk factors as hypertension, DM, smoking, and family history (variables believed to cause confounding) were equally distributed (matched) among both studied groups to adjust for confounding[11]. All enrolled participants completed the study and there were no withdrawals.

Bisphenol was detected in serum using a Bisphenol A ELISA kit from MYBIOSOURCE with a detection range 200 ng/mL-3.12 ng/mL and sensitivity of Up to 0.6 ng/mL which was the cutoff used to define detection of bisphenol A in serum of subjects.

2. Dilated cardiomyopathy and ELECTROCARDIOGRAM

The percent of patients in the DCM group who had ECG abnormalities was 50%, while the percent of patients in the healthy control group who had ECG abnormalities was 10%, respectively (Table 2). There was a statistically significant moderate association between DCM and ECG abnormalities ($X^2 = 13.2$, $P = 0.0003$, $V = 0.406$).

3. Dilated cardiomyopathy and Bisphenol A

The percent of patients in the DCM group who were exposed to BPA was 24%, while the percent of patients in the healthy control group who were exposed to BPA was 6.7%, respectively (Table 3). There was a statistically significant weak association between BPA exposure and DCM ($X^2 = 3.9$, $P = 0.048$, $V = 0.221$).

4. Bisphenol A and heart failure

In the DCM group, the percent of patients who were New York Heart Association (NYHA) class II was 44%, the percent of patients who were NYHA class III was 34%, and the percent of patients who were NYHA class IV was 22%, respectively (Table 4). There was a non-significant association between BPA exposure and the NYHA classification of HF ($X^2 = 2.5$, $P = 0.280$).

5. Bisphenol A and volumetric indexes of the left atrial diameter and right ventricular size and function

In the DCM group, there was a statistically significant difference in the LA diameter of the study participants exposed to BPA versus not exposed to BPA ($t(48) = 3.19$, $P = 0.050$), a highly significant strong association between BPA exposure and RV dilatation ($X^2 = 17.3$, $P = < 0.0001$, $V = 0.588$), and a highly significant difference in the TAPSE of the study ($t(48) = –3.16$, $P = < 0.0001$) (Table 5).

Discussion

Recent epidemiological studies have detected BPA in contaminated food and drinking water, wastewater, air and dust particles with an overall 90% prevalence rate of environmental and occupational exposure to BPA and its analogues[12].

Table 1 - Comparison between dilated cardiomyopathy and healthy controls groups regarding the baseline characteristics and risk factors.

		Dilated Cardiomyopathy Group No: 50	Healthy Controls Group No: 30	Independent t-test	P value
Age Mean ± SD		56.7 ± 12.8	58.2 ± 9.8	1.5	0.568
		Dilated Cardiomyopathy Group	Healthy Controls Group	Chi-square test	P value
		No: 50	No: 30		
Sex	Females	13 (26.0%)	7 (23.3%)	0.07	0.790
	Males	37 (74.0%)	23 (76.7%)		
Residence	Fayoum	17 (34.0%)	10 (33.0%)	0.004	0.951
	Other Districts	33 (66.0%)	20 (66.7%)		
No: of Offspring	0	2 (4.0%)	0 (0.0%)	1.99	0.574
	2	12 (24.0%)	5 (16.7%)		
	3	13 (26.0%)	9 (30.0%)		
	≥4	23 (46.0%)	16 (53.3%)		
Diabetes Mellitus	Yes	9 (18.0%)	8 (26.7%)	0.84	0.359
	No	41 (82.0%)	22 (73.3%)		
Hypertension	Yes	14 (28.0%)	9 (30.0%)	0.0366	0.848
	No	36 (72.0%)	21 (70.0%)		
Smoking	Ex-smokers	15 (30.0%)	8 (26.7%)	2.37	0.306
	Smokers	3 (6.0%)	5 (16.7%)		
	Non-smokers	32 (64.0%)	17 (56.7%)		
Family History	Yes	9 (18.0%)	8 (26.7%)	0.84	0.359
	No	41 (82.0%)	22 (73.3%)		

Table 2 - Comparison between dilated cardiomyopathy and healthy controls groups regarding the ECG abnormalities.

		Dilated Cardiomyopathy Group No: 50	Healthy Controls Group No: 30	Chi-square test	P value
ECG Characteristics	Normal ECG	25 (50.0%)	27 (90.0%)	13.2	0.0003
	Abnormal ECG including Atrial Fibrillation, Left Bundle Branch Block, and Right Bundle Branch Block	25 (50.0%)	3 (10.0%)		

Table 3 - Comparison between dilated cardiomyopathy and healthy controls groups regarding Bisphenol A.

	Dilated Cardiomyopathy Group No: 50	Healthy Controls Group No: 30	Chi-square test	P value
Bisphenol A detected	12 (24.0%)	2 (6.7%)	3.9	0.048
Bisphenol A not detected	38 (76.0%)	28 (93.3%)		

Table 4 - Association between Bisphenol A and New York Heart Association classification of heart failure in patients with dilated cardiomyopathy

	Dilated Cardiomyopathy with detected Bisphenol A No: 12	Dilated Cardiomyopathy with non-detected Bisphenol A No: 38	Chi-square test	P value
New York Heart Association Class II	5 (41.7%)	17 (44.7%)	2.5	0.280
New York Heart Association Class III	6 (50.0%)	11 (28.9%)		
New York Heart Association Class IV	1 (8.3%)	10 (26.3%)		

Table 5 - Association between Bisphenol A and volumetric indexes of the left atrial diameter and right ventricular size and function in patients with dilated cardiomyopathy.

		Dilated Cardiomyopathy with detected Bisphenol A No: 12	Dilated Cardiomyopathy with non-detected Bisphenol A No: 38	Independent t-test	P value
Left Atrial Diameter Mean ± SD		40.58 ± 4.34	37.39 ± 5.55	3.19	0.050
		Dilated Cardiomyopathy with detected Bisphenol A	Dilated Cardiomyopathy with non-detected Bisphenol A	Chi-square test	P value
		No: 12	No: 38		
Right Ventricle Size	Dilated Right Ventricle	9 (75.0%)	5 (13.2%)	17.3	< 0.0001
	Normal Right Ventricle	3 (25.0%)	33 (86.8%)		
		Dilated Cardiomyopathy with detected Bisphenol A	Dilated Cardiomyopathy with non-detected Bisphenol A	Independent t-test	P value
		No: 12	No: 38		
Tricuspid Annular Plane Systolic Excursion Mean ± SD		14.42 ± 1.93	17.58 ± 2.32	–3.16	< 0.0001

In 2012, the National Institute of Environmental Health Sciences and National Toxicology Program harmonized a consortium-based approach to address the gaps in research on the health effects of BPA[13].

Three years later, Xiong et al investigated the association between BPA exposure and cardiovascular diseases.

They demonstrated increased serum levels of BPA in DCM patients compared with healthy controls.

Another study by Posnack et al. has concluded significant impairment of cardiac contractility in male and female rats when exposed to environmentally relevant doses of BPA[14].

Our study compared the BPA serum levels between healthy controls and DCM patients. It included 80 patients in whom, 50 were DCM and 30 were controls. In our study, BPA was significantly more detected (P:0.04) among DCM patients than the healthy control group. Our study's results were consistent with Xiong et al study.

As noted above, the percent of patients in the DCM group who were exposed to BPA was 24%, while the percent of patients in the healthy control group who were exposed to BPA was 6.7%, respectively, confirming a statistically significant association between BPA exposure and DCM.

The association between the impaired cardiac function in rats and exposure to BPA addressed in Posnack et al. animal study might explain our study's findings of a significant decline in the RV function when DCM patients are exposed to BPA.

Correlation between laboratory and echocardiographic findings among DCM patients found that in participants exposed to BPA, the RV functions and dimensions were more affected than those not exposed to BPA with significant difference in TAPSE. (P = < 0.0001).

Also, the LA diameter showed statistically significant difference (p=0.050) between patients exposed versus non exposed to BPA. These findings highlight the generalized cardiac effect of BPA exposure not only on the LV.

The pathogenesis involves epigenetic changes, nuclear receptogeneralized cardiac in male anieexpexposure note to BPA for long time caused hypermethylation and decreased expression of Peroxisome proliferator activated receptor γ co-activator one alfa.

Treatment of pregnant female animal models with BPA from the 6th gestational day to just before delivery and from the first day after delivery to the end of the third week, caused inflammatory cellular infiltration and a focal fibrosis resulting in increased incidence and increased severity of cardiomyopathy[16].

BPA was more detected in patients with DCM highlighting the possibility of an association between them. This rises the need of limitation of using plastics and other manufactured material from BPA and the use of other alternative to BPA in carbonated materials and plastic industries.

Strengths and limitations

Our study was conducted on a well-balanced cohort with respect to baseline characteristics, risk factors, and NYHA class, with no missing data, enabling a robust per-protocol analysis. Echocardiographic outcomes were assessed and reported by investigators who were blinded to participant identity and laboratory results, thereby minimizing observer bias. To the best of our knowledge, the association between BPA exposure and volumetric indices of LA diameter as well as RV size and function in patients with DCM has not been previously investigated. Despite its strengths, the study limitations require consideration. It was a single centre cross-sectional study with a small sample size which didn't allow us to investigate a causal relationship between the echocardiographic assessment outcomes and retrospective BPA exposure in patients with DCM vs healthy controls.

BPA exposure can vary depending on many factors including occupation, income and preferences which can affect how often people use plastic containers in cooking and storing food.

Conclusions

The prevalence of BPA exposure was more in patients with DCM vs healthy controls and the volumetric indexes of the LA diameter, and the RV size and function were worse in patients with DCM exposed to BPA versus patients with DCM not exposed to BPA.

What this study adds (what's new):

- The association between BPA exposure and DCM is an observation which warrants further research as a case-control study to determine if there is a causal relationship between BPA exposure and DCM.
- Recommending use of BPA industrial alternatives in food and beverage containers.
- Recommending public campaigns to raise awareness about BPA environmental and health hazards.

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Conflict of Interest

None

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