Association of Exposure to Bisphenol A and Incidence of Cardiovascular Disease and Hypertension

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Bisphenol A (BPA) is an industrial chemical used in the production of polycarbonate, a hard, clear, plastic and epoxy resin, which is used in the production of plastic bottles, cans, dental fillings and resins for the inner coating of cans.[1] Due to its wide use in the United States and elsewhere, BPA exposure is ubiquitous and has been detected in 95% of the US population.[2] Its use in food and drink containers has been considered safe for the consumers of such foods and drinks but recent studies have raised concerns, because BPA leaches into the food or drinks and their consumption has been shown in recent studies to be associated with an increased incidence of cardiovascular disease (CVD), hypertension (HTN), obesity, and diabetes.[3–6] In addition, BPA is considered to be an endocrine-disrupting chemical and has been shown to have an affinity for the estrogen receptors α and β[7,8] and could affect the function of the cardiovascular system since the myocardial cells possess estrogen receptors α and β. These receptors have antiatherogenic actions, cause vasodilation, preserve vascular integrity and cardiomyocyte survival, and regulate the excitability of smooth muscle cells.[9,10] These findings have created anxiety and fear regarding the consumption of foods and drinks in containers made of BPA. However, a recent (2014) review on the subject by the safety committee of the Food and Drug Administration concluded that BPA in the current doses used is safe for human consumption.[1] To better understand the ramifications of BPA exposure, a Medline search of the English language literature was conducted between 2010 and 2014, and of the 62 abstracts reviewed, 14 pertinent papers were selected and these papers together with collateral literature will be discussed in this editorial.

ASSOCIATION OF URINARY BPA LEVELS AND INCIDENCE OF CVD AND HTN

Several studies have shown an association between urinary BPA levels and incidence of CVD and HTN. The findings from these studies are summarized in the Table and briefly discussed here.

A study by Carwile and Michels[6] was a cross-sectional analysis of urinary BPA and incidence of obesity in 2747 adults aged 18 to 74 years from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and 2005–2006 studies. The creatinine-adjusted geometric mean of urinary BPA concentration was divided in quartiles (Q) 1 through 4. With Q1 being the referent, the OR for the presence of obesity in Q2 was 1.72 (95% CI, 1.27–2.34, urinary BPA 1.2–2.3 ng/mL); in Q3 was 1.30 (95% CI, 0.88–1.92, urinary BPA 2.4–4.6 ng/mL); and in Q4 was 1.34 (95% CI, 0.81–2.22, urinary BPA ≥4.7 ng/mL).

A trial by Melzer and colleagues[11] was a prospective cohort study from the European Prospective Investigation of Cancer-Norfolk UK, which included 758 patients with incident coronary artery disease (CAD) and 861 controls aged 40 to 74 years, free of CAD, stroke, or diabetes mellitus at baseline. After 10.8 years of follow-up, the OR for CAD after multiple adjustments was 1.13 (95% CI, 1.01–1.25, urinary BPA 1.3 ng/mL).

A study by Bae and colleagues[12] correlated urinary BPA levels in 560 elderly persons with a mean age of 70.6±5.2 years with heart rate variability (HRV) and blood pressure (BP) between 2008 and 2010. Of the 560 participants, 521 were included in the analysis. Mean urinary BPA concentration was 1.2 μg/g creatinine and the OR for incident hypertension for 258 nonhypertensive patients at baseline was 2.35 (95% CI, 1.33–4.17). There was no association between urinary BPA levels and HRV.

A study by Shankar and Teppala[13] investigated the association of urinary BPA levels and incidence of hypertension in a sample of 1300 patients from NHANES 2003–2004 with a mean age of 46.2±0.5 years. The patients were divided into tertiles, with tertile 1 being the referent. The OR for incidence of hypertension (systolic BP >140 mm Hg or diastolic BP >90 mm Hg) after multivariable adjustments for tertile 2 was 1.11 (95% CI, 0.71–1.74, urinary BPA 1.5–4.0 ng/mL) and for tertile 3 was 1.50 (95% CI, 1.12–2.00, urinary BPA >4.0 ng/mL).

A study by Melzer and colleagues[13] investigated the association of urinary BPA levels and the incidence of angiographically proven CAD in 591 patients aged 58 to 95 years from the Metabonomics and Genomics in Coronary Artery Disease (MaGiCAD) trial in Cambridgeshire United Kingdom. Of these, 385 patients had severe CAD (1- to 3-vessel), 86 had intermediate, and 120 had normal coronary arteries. The unadjusted median urinary BPA concentration was 1.28 ng/mL for patients with normal coronary arteries and 1.53 ng/mL for those with severe CAD. The OR for severe CAD was 1.43 (95% CI, 1.03–1.98; *P*=.003) and borderline significant for intermediate CAD (OR, 1.69; 95% CI, 0.98–2.94; *P*=.061).

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TABLE. Association of Exposure to BPA and Incidence of CAD and HTN

	Patients, No.	Age, y	Disease	BPA, ng/mL	OR (95% CI)
Carwile[6]	2747	18–74	Obesity	Q2 1.2–2.3	1.72 (1.27–2.34)
				Q3 2.4–4.6	1.30 (0.88–1.92)
				Q4≥4.7	1.34 (0.81–2.22)
Melzer[11]	1599	40–74	CAD	1.3	1.13 (1.01–1.25
Bae[12]	560	70.6±5.2	HTN	1.2 μg/g Cr	2.35 (1.33–4.17)
Shankar[13]	1300	46.2±0.5	HTN	Ter 2 1.5–4.0	1.11 (0.71–1.74)
				Ter 3 >4.0	1.50 (1.12–2.00)
Melzer[14]	591	58–95	CAD	1.28	1.43 (1.03–1.98)
Shankar[4]	745	55.9±7	PAD	Ter 2: 1.4–3.6	1.10 (0.22–5.39)
				Ter 3: >3.6	2.69 (1.02–7.09)
Bae[5]	60	73.1±4.2	HTN	16.9 ng SBP CC>GG (P<.016)	

Abbreviations: BPA, bisphenol A; CAD, coronary artery disease; CC, two cans; CI, confidence interval; Cr, creatinine; GG, two glass bottles; HTN, hypertension; OR, odds ratio; PAD, peripheral arterial disease; SBP, systolic blood pressure.

Quartile (Q) 1 and tertile (Ter) 1 were considered as referents.

A study by Shankar and colleagues[4] investigated the association of BPA urinary levels with the incidence of peripheral vascular disease (PAD) in a sample of 745 patients with a mean age of 55.9±0.7 years from NHANES 2003–2004. They found a positive association between urinary BPA levels 1.4–3.6 ng/mL for tertile 2 (OR, 1.10; CI, 0.22–5.39) and urinary BPA levels >3.6 ng/mL for tertile 3 (OR, 2.69; CI, 1.02–7.09) after multivariable adjustments. Tertile 1 was considered as referent.

In a recent study, Bae and Hong[5] investigated the acute effects of BPA consumption on BP and HRV. In this study, 60 older patients with a mean age of 73.1±4.2 years were asked to drink soy milk packaged in either glass bottles made of BPA or cans lined with BPA. The patients visited the clinic three times weekly and each time they were given either two cans (CC), two glass bottles (GG), or one can and one glass bottle (CG) to drink. BPA levels were measured in the cans and bottles as well as in urine samples given by the study participants. The mean BPA concentration measured from the glass bottles and cans were 0. 031±0.01 ng/mL and 8.2±0.82 ng/mL. The urinary BPA concentration was significantly higher after consuming drinks in CC or CG compared with GG (P<.0001). In addition, systolic BP was 5 mm Hg higher in participants who consumed drinks in CC compared with those who consumed drinks in GG (P<.016). There was no significant effect in HRV between those who consumed drinks in CC, CG, or GG.

DISCUSSION

BPA is one of the highest volume chemicals produced worldwide, with about 6 billion pounds produced annually.[15] This chemical is used in the manufacturing of plastic bottles and resins for the inner lining of cans to protect contact of the food and drinks with the surface of the cans. Therefore, the human exposure is ubiquitous and BPA has been detected by the Centers for Disease Control and Prevention in the urine of 92.6% of 2517 adults in the US population[16] and in 95% in a previous sample of 354 US adults.[2] In addition, BPA was detected in 63 of 105 (60%) canned food samples with levels ranging from 0.23 ng/g ww to 65.0 ng/g ww.[17] The US Environmental Protection Agency (EPA) has established a safe daily intake of BPA of 50 μg/kg bw based on the assumption that the main source of exposure is oral through food ingestion.[18] In contrast, the European Union has set the maximum tolerable daily intake of BPA at 10 μg/kg bw.[15] It has also been demonstrated that prolonged storage of cans could increase the leaching of BPA into the food. A study by the Harvard School of Public Health showed in a crossover study of 75 healthy volunteers aged 27 to 51 years fed canned soup had significantly higher urinary BPA levels than those fed the same freshly prepared soup.[19] The adjusted geometric mean concentration of urinary BPA was 1.1 μg/L (95% CI, 0.9–1.4 μg/L) after fresh soup consumption and 20.8 μg/L (95% CI, 17.9–24.1 μg/L) after consumption of canned soup, a 1221% increase. Urinary samples are the best way to measure BPA exposure because BPA is rapidly glucoronated in the liver after absorption and is excreted in the urine. Therefore, it has been suggested that BPA could cause harm after frequent and prolonged exposure to the chemical.[18] Although, both the US EPA and the European Food Safety Authority have declared that BPA is safe in the current doses recommended,[1,20] recent scientific evidence suggests that BPA may not be safe since it has been associated with HTN, CAD, PAD, obesity, and diabetes mellitus.[3–6,21] In addition, the recent scientific statement by the Endocrine Society[18] is a cause for concern for public safety. According to the Society's statement, chemicals with endocrine-disrupting actions such as BPA, besides being implicated in the cause of HTN, CVD, obesity, and diabetes mellitus, could also interfere with hormone biosynthesis and effects on

male and female reproduction, breast development and cancer, prostate cancer, and thyroid metabolism. However, skeptics believe that research data come from animal studies, which is not applicable to human data, and that most human data come from one population from NHANES. However, data are continuously coming from other populations and the evidence is becoming more robust regarding the human safety of BPA. In order to gain a better perspective of the human safety of BPA, well-coordinated, prospective studies are needed.

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