REVIEW ARTICLE

Bisphenol A, obesity, and type 2 diabetes mellitus: genuine concern or unnecessary preoccupation?

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Bisphenol A (BPA) is a ubiquitous industrial chemical found in a variety of plastic containers intended for food storage and in the epoxy resin linings of metal food and beverage cans, where it is used to prevent corrosion, food contamination, and spoilage. BPA has been linked recently to a wide variety of medical disorders and is known to have estrogenic activity with genomic as well as nongenomic estrogen receptor-mediated effects. Given the rapidly increasing prevalence rates of metabolic disorders such as obesity and type 2 diabetes, BPA has come under recent intense scrutiny in scientific and lay communities as a potential endocrine-disrupting compound with diabetogenic effects. The purpose of this review is to examine critically the available literature investigating the link between BPA and alterations in metabolic health. Typical levels of exposure to BPA in daily life are discussed, and both epidemiologic human data and mechanistic preclinical studies that have tested associations between BPA and obesity and diabetes are analyzed. Last, current policies and views of national and international regulatory agencies regarding the safety of BPA use are summarized. (Translational Research 2014;164:13–21)

Abbreviations: BPA = bisphenol A; EDC = endocrine-disrupting chemical; FDA = Food and Drug Administration; NHANES = National Health and Nutrition Examination Survey; T2D = type 2 diabetes; WHO = World Health Organization

Diabetes mellitus is a disease of disordered glucose homeostasis that affects more than 300 million individuals worldwide and roughly 26 million Americans. Type 2 diabetes (T2D) accounts for approximately 90% of all diabetes cases and is characterized by a combination of insulin resistance, impaired hepatic gluconeogenesis, and altered β-cell function.[1,2] The prevalence of T2D in U.S. adults has nearly tripled since 1980,[3] and recent data suggest T2D is increasingly prevalent among younger populations.[4] These trends have been attributed primarily to the growing and parallel epidemic of obesity. Although overnutrition and lack of physical activity play a central role in the pathophysiology of obesity and diabetes, there is increasing attention in both scientific and lay communities regarding the effects of

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environmental toxins on overall metabolic health. Chemicals and pollutants such as lead, arsenic, polychlorinated biphenyls, dioxins, dichlorodiphenyltrichloroethane, and phthalates have all been classified as potential endocrine-disrupting chemicals (EDCs),[5,6,7] which the World Health Organization (WHO) defines as any "exogenous substance or mixture that alters function of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations."[8]

Bisphenol A (BPA) is a ubiquitous chemical that is garnering focused scrutiny as a potentially diabetogenic EDC. BPA is an industrial chemical that has been used widely since the 1960s to produce plastics; its primary purpose is to prevent damage to polycarbonate containers through multiple uses. BPA is also used in the epoxy resin linings of metal food and beverage cans to prevent corrosion, food contamination, and spoilage.[9,10] In 2012, the U.S. Food and Drug Administration (FDA) banned the use of BPA in products designed for infants and toddlers because of consumer concerns of its effects on neurologic development in young children. However, currently, the FDA maintains that small levels of BPA, such as those found in canned food, are safe for consumption.[10] However, there is ongoing controversy regarding the background amount of BPA exposure in modern society as well as the establishment of safe levels of exposure. Despite growing concerns surrounding BPA toxicity, a study by Transparency Market Research[11] suggests the demand for BPA in products has been increasing, and BPA sales are expected to increase to almost $19 billion by the year 2019. One of the reasons for this anticipated increase is growing industrialization in many Asian countries, such as China.[12] The goal of this review is to summarize human epidemiologic and preclinical mechanistic studies that have investigated links between BPA and the development of glucose intolerance and obesity, suggest steps that can be taken to further research in this area, and provide ways in which consumers can minimize contact with BPA.

HUMAN EXPOSURE TO BPA

Humans come in contact with BPA through residual industrial waste in air and water. However, the most common medium for BPA exposure is through consumption of food stored in BPA-containing containers. BPA found in the epoxy resin lining of metal cans and in polycarbonate plastics can leach into the food or drink inside the container. The amount of BPA that migrates into food depends on the amount of BPA used to make the material, as well as the heating times and temperatures used to manufacture the container. Increased BPA levels have been shown to leach into food if the container is placed in a microwave for extended periods of time, or exposed to vegetable oil and/or sodium chloride solutions.[13,14]

Whether humans are exposed to enough BPA to cause ill effects is highly controversial, and there is disagreement surrounding how much BPA humans are exposed to on a daily basis. The FDA estimates that infants are exposed to 0.2–0.4 μg/kg body weight of BPA/day, whereas children and adults are exposed to 0.1–0.2 μg/kg/day.[10] On the other hand, the WHO estimates that infants can be exposed to as much as 0.45–1.61 μg/kg/day and toddlers can be exposed to as much as 0.78 μg/kg/day.[15] However, there is a general consensus that infants and toddlers are exposed to more BPA than adults on a regular basis. These differences may be secondary to increased levels of ingestion when normalized to body weight, and an increased tendency for infants and toddlers to place objects in their mouth.[16]

Data from the 2003–2004 U.S. National Health and Nutrition Examination Survey (NHANES) demonstrated that approximately 90% of the U.S. population 6 years of age and older had detectable levels of BPA in their urine, with concentrations ranging from 0.4 μg/L to 149 μg/L. Children and adolescents had greater urinary BPA levels compared with adults, a finding consistent with increased levels of exposure.[17] Important ethnic and socioeconomic differences have also been noted, and those in the lowest income categories had the highest levels of urinary BPA.[18] BPA has also been detected in breast milk and fetal cord blood.[19,20]

EPIDEMIOLOGIC DATA SHOWING CORRELATIONS BETWEEN BPA AND OBESITY AND DIABETES

During the past 10 years, a number of studies have linked BPA to detrimental health effects that are broad in scope and include cancer, neurologic disorders, and infertility.[21-23] The correlation between urinary BPA concentrations from NHANES data and obesity and diabetes has been tested by a number of groups. Lang et al[24] analyzed the relationship between urinary BPA and diabetes using cross-sectional NHANES data from 2003–2004. They found higher levels of BPA were associated positively with a self-reported diagnosis of either diabetes or "borderline diabetes." Citing some specificity to metabolic outcomes, the group did not find an association between urinary BPA and other chronic diseases such as asthma, cancer, or chronic bronchitis.[24] Melzer et al[25] analyzed data subsequently from the 2003–2004 and 2005–2006 NHANES data sets and found a significant association between urinary BPA levels and diabetes in pooled data. However, the