Association of urinary phenolic compounds, inflammatory bowel disease and chronic diarrheal symptoms: Evidence from the National Health and Nutrition Examination Survey ☆

Punyanganie S. de Silva, MD, MPH, MRCP(UK) [a, *], Xuan Yang, MHS, MPH [b],
Joshua R. Korzenik, MD [a], Rose H. Goldman, MD, MPH [c], Kristopher L. Arheart, EdD [d],
Alberto J. Caban-Martinez, DO, PhD, MPH [b, c, d, e]

[a] Division of Gastroenterology, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115, United States
[b] Division of Environment and Public Health of the Department of Public Health Sciences, University of Miami, Miller School of Medicine, Miami, FL 33136, United States
[c] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA 02115, United States
[d] Division of Biostatistics of the Department of Public Health Sciences, University of Miami, Miller School of Medicine, Miami, FL 33136, United States
[e] Department of Orthopedic Surgery, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115, United States

ARTICLE INFO

ABSTRACT

Endocrine disruptors such as phenolic compounds and parabens may be involved in chronic non-infective disease. While products incorporating these compounds are extensively utilized in consumer and personal products, little is known about their effect on bowel health. Inflammatory bowel disease (IBD) - consisting of the diseases ulcerative colitis and Crohn's disease - and irritable bowel syndrome are common chronic non-infectious diarrheal diseases. Despite limited knowledge on the etiology of IBD, these diseases have increased prevalence in industrialized countries and cause significant impairment to quality of life. In the present study we examine relationships between urinary environmental phenolic compounds, chronic diarrhea and inflammatory bowel disease. Data was obtained from the 2005–2010 US National Health and Nutrition Examination Survey (NHANES) including demographics, lifestyle factors, self-reported health conditions, inflammatory markers and urinary phenolic chemical concentrations. Only participants with complete environmental phenols & parabens component were included in our analysis. Chronic diarrheal symptoms were determined by using the 2009–2010 NHANES questionnaire which included questions pertaining to bowel health. We utilized chronic bowel leakage symptoms as a surrogate marker for chronic diarrhea. The presence of IBD was also analyzed from 2009 to 2010 NHANES data, as a sub-analysis for arthropathy directly querying the presence or absence of IBD. Among the subset of 5218 American adults aged 20–80 years in the NHANES study period who completed environmental phenols & parabens component, 25.5% reported chronic diarrheal symptoms. Abnormal markers of inflammation were present in 2200 (42.2%) of respondents. For IBD, 19 individuals with arthropathy confirmed a diagnosis of ulcerative colitis, and 1 person confirmed a Crohn's diagnosis. After adjustment for demographics, inflammatory and subsample weighing; lower paraben levels were associated with chronic bowel leakage (diarrheal) symptoms. Higher 4-tert-octylphenol levels was significantly associated with ulcerative colitis. Further study of underlying mechanisms should be considered.

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1. Introduction

Chronic diarrheal illness is highly prevalent in the United States with reports of prevalence ranging from 11 to 30% of the overall population (AE et al., 2015; Grundmann and Yoon, 2010). Non-infectious causes of chronic diarrhea can broadly be classified

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into irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD). Both conditions can lead to significant deterioration in quality of life and absence from work (Zand et al., 2015).

The majority of patients with IBS present with chronic diarrheal symptoms (IBS-D), and recent data suggests that IBS-D is increasing, with 10–20% of adults in the United States suffering from symptoms of chronic functional diarrhea (Saito et al., 2002; Thompson et al., 2002). An increase in hospitalizations for IBS symptoms was also noted from 1997 to 2010 (Sethi et al., 2013).

IBS impacts most substantially on patients' work and social life. It has been reported that on average patients would sacrifice between 10 and 15 years of their remaining life expectancy for an immediate cure with up to 43% of patients paying for remedies. No studies quantify loss of earnings related to IBS but direct care costs are substantial with annual international estimates per patient of: USA $742-$7547, UK £90-£316, France €567-€862, Canada $259 and Germany €791. Cost to industry internationally through absenteeism related to IBS is estimated between £400 and £900 per patient annually (Canavan et al., 2014).

IBD consists of a broad spectrum of chronic immune mediated disorders of the intestine. Although pathogenesis was previously thought to be primarily genetic, despite considerable advances in identifying IBD specific risk loci, disease risk is not completely accounted for, thereby supporting a role for environmental risk factors in disease pathogenesis (Wang and Achkar, 2015).

To further support this hypothesis of environmental risk factors, a recent systematic review of disease incidence and prevalence noted that there is an increasing incidence of IBD in countries that were previously perceived to have low genetic risk for both UC and CD (Molodecky et al., 2012).

Phenolic compounds are commonly found in the environment, and are recognized as chemical estrogens or endocrine disruptors (EDC). Humans experience ubiquitous exposure to phenols from the environment, including bisphenol A (BPA) and parabens (Vandenberg et al., 2007; Dodge et al., 2015). These chemicals are found in a variety of products in common use, such as topical pharmaceutical preparations, self-hygiene products such as cleansers, antiperspirants, toothpastes and soaps, along with certain food products such as marinated fish, canned products and certain processed foods., *The National Report on Human Exposure to Environmental Chemicals* which is periodically issued by the Centers for Disease Control and Prevention detected BPA in 92.6% of a nationally representative sample (Calafat et al., 2008). Methyl and propyl paraben were detected in 99.1% and 92.7%, respectively (Calafat et al., 2010).

Exposure to phenols and parabens is from oral or transdermal routes, and urinary concentrations of these compounds can be used as biomarkers of their exposure (Calafat et al., 2010).

Recent studies have suggested that certain phenolic compounds such as BPA are hormonally active at low doses (Vandenberg et al., 2007), thereby raising the possibility of their risk to human health. Estrogen receptors are also found in the colonic mucosa and a recent animal model noted that BPA administration prenatally led to an increased pro-inflammatory response in the colon of female offspring (Braniste et al., 2010).

It has also been demonstrated that commonly found EDCs which include triclosan and the parabens have antimicrobial properties (Savage et al., 2012), and some parabens are also known to destabilize microbial membranes (Bredin et al., 2005). Several studies using culture-based and culture-independent methods have shown that fecal microbiota differs between IBS patients and healthy controls (Carroll et al., 2011; Malinen et al., 2005; Mättö et al., 2005). In addition, other studies have also suggested associations between certain commensal human bacterial flora and inflammatory bowel disease (Lavelle et al., 2015; Toumi et al., 2014).

Therefore, it is plausible that EDCs with antimicrobial properties may modify an individual's risk for IBD or IBS by altering the human microbiome.

The aim of this study was therefore to assess whether differences in exposure to phenolic compounds as measured by urinary concentrations, in a national sample of U.S. adults is associated with differences in chronic diarrheal illness and inflammatory bowel disease. We hypothesize that individuals with higher urinary phenoloic compounds may have higher symptoms or greater proportion of disease than those with low to no phenolic compound exposures.

2. Materials & methods

Secondary analysis was performed on data previously collected through the National Health and Nutrition Examination Survey (NHANES), a biennial cross-sectional survey designed to assess the health and nutritional status of adults and children in the United States (Zand et al., 2015). NHANES data were obtained through a publicly accessible archive at the National Center for Health Statistics. Data were aggregated from participants of the 2005–2006, 2007–2008, and 2009–2010 NHANES survey periods who had completed both the environmental phenols and home urine exam. Due to the eligibility criteria of the home urine exam, all participants were age 6 years and older; however for our analyses we retained adults age 20 years and older.

The entire study sample included all adults 20 years and older who completed the environmental phenols & parabens survey component from three NHANES waves (2005–2006, 2007–2008 and 2009–2010). Of the 5218 total participants from the pooled three survey periods, 4932 participants had complete laboratory data for markers of inflammation. A total of 4721 of these adults aged 20 years and older were also interviewed for symptoms pertaining to bowel health. Questions assessing inflammatory bowel disease were not included in the 2005–2006 and 2007–2008 surveys. Inflammatory bowel disease data was limited to the 2009–2010 survey; therefore, analysis of bowel disease was only performed on 2009–2010 survey data. In the final analysis 2749 participants age 20–69 were included in the analysis of bowel disease. Weighted estimates were also obtained and extrapolated to the sample data in order to obtain nation wide estimated values.

The NHANES data included monitoring of exposure to a variety of environmental toxins, including phenols and parabens. About one fourth of the subjects in the pooled study database were randomly selected to provide urine samples for environmental phenols testing. Urine specimens were analyzed at the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention. For each chemical concentration below the limit of detection (LOD), NHANES replaced it by value of LOD divided by the square root of two.

Statistical analysis was performed to test for significant differences in urinary paraben and phenol levels in patients stratified based on three conditions: 1) normal or abnormal levels of inflammatory markers; 2) absence of presence of bowel leakage (a substitute for diarrhea); and 3) presence or absence of known inflammatory bowel disease. T-test was performed to compare the levels of chemical concentrations, with $p < 0.05$ considered to be statistically significant. Covariate analysis was performed using age, race, gender, marital status, and annual household income. Two subsequent analysis were performed – a poisson regression to assess the relationship between the number of bowel leakage symptoms and parabens and phenols levels, and a logistic regression to estimate the odds of having elevated paraben and phenol levels in participants with and without inflammatory bowel