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Acrolein metabolites, diabetes and insulin resistance

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ABSTRACT

Acrolein is a dietary and environmental pollutant that has been associated *in vitro* to dysregulate glucose transport. We investigated the association of urinary acrolein metabolites N-acetyl-S-(3-hydroxypropyl)-L-cysteine (3-HPMA) and N-acetyl-S-(carboxyethyl)-L-cysteine (CEMA) and their molar sum (∑acrolein) with diabetes using data from investigated 2027 adults who participated in the 2005–2006 National Health and Nutrition Examination Survey (NHANES). After excluding participants taking insulin or other diabetes medication we, further, investigated the association of the compounds with insulin resistance (n = 850), as a categorical outcome expressed by the homeostatic model assessment (HOMA-IR > 2.6). As secondary analyses, we investigated the association of the compounds with HOMA-IR, HOMA-β, fasting insulin and fasting plasma glucose. The analyses were performed using urinary creatinine as independent variable in the models, and, as sensitivity analyses, the compounds were used as creatinine corrected variables. Diabetes as well as insulin resistance (defined as HOMA-IR > 2.6) were positively associated with the 3-HPMA, CEMA and ∑Acrolein with evidence of a dose-response relationship ($p < 0.05$). The highest 3rd and 4th quartiles of CEMA compared to the lowest quartile were significantly associated with higher HOMA-IR, HOMA-β and fasting insulin with a dose-response relationship. The highest 3rd quartile of 3-HPMA and ∑Acrolein were positively and significantly associated with HOMA-IR, HOMA-β and fasting insulin. These results suggest a need of further studies to fully understand the implications of acrolein with type 2 diabetes and insulin

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1. Introduction

Acrolein, an α,β-unsaturated aldehyde, is a common dietary and environmental pollutant and is released in the environment from combustion of petroleum fuels, biodiesel, plastic, paper and wood, and is a major component of tobacco smoke (Agency for Toxic Substances and Disease Registry, 2007). Dietary sources of acrolein are generated during the heating of vegetable oils and animal fats and acrolein is also present in beverages such as coffee and alcohol (Alwis et al., 2015; Agency for Toxic Substances and Disease Registry, 2007). Furthermore, acrolein is endogenously generated during lipid peroxidation, amine oxidase-mediated metabolism of polyamines, and myeloperoxidase (Moghe et al., 2015). Acrolein is highly water soluble, enabling it to rapidly enter body tissues and form conjugates with cellular glutathione (GSH). Upon conjugation, acrolein is further metabolized into N-acetyl-S-(carboxyethyl)-L-cysteine (CEMA) or catalyzed in N-acetyl-S-(3-hydroxypropyl)-L-cysteine (3-HPMA), the main urinary metabolite of acrolein (Abraham et al., 2011; Moghe et al., 2015; Stevens and Maier et al., 2008).

Acrolein is a respiratory toxicant and has been associated with a number of health complications, including pulmonary edema, increased bronchial responsiveness (Agency for Toxic Substances and Disease Registry, 2007) and may have a role in chronic obstructive pulmonary disease (Bein and Leikauf, 2011). It has also been associated with atherosclerosis (Park and Taniguchi, 2008) and increased risk of cardiovascular disease (DeJarnett et al., 2014), Alzheimer's disease (Dang et al., 2010) and multiple sclerosis (Tully and Shi, 2013). Furthermore acrolein protein adducts have been associated with diabetic complications such as diabetic nephropathy (Suzuki and Miyata, 1999) and diabetic retinopathy (Grigsby et al., 2012). Two studies report an association between acrolein with type 2 diabetes (Daimon et al., 2003) or type 1 diabetes (Tsukahara et al., 2003). Recently, acrolein has been associated with dysregulation of glucose transport in human endothelial cells (O'Toole et al., 2014). The incidence of diabetes mellitus, particularly type 2 diabetes, is increasing worldwide (Danaei et al., 2011). In the United States, diabetes is estimated to affect 8.3% of the total population and 11.3% of the adult

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population 20 years and older. Along with age, family history, genetic variants, obesity, physical inactivity and smoking, environmental pollutants have also been associated with type 2 diabetes (Kuo et al., 2013). Due to the molecular evidence of acrolein effects on dysregulation of glucose transport, the objective of this study was to investigate whether urinary acrolein metabolites, 3-HPMA and CEMA, are associated with type 2 diabetes and insulin resistance in adults (20 years and older) using 2005-2006 National Health and Nutrition Examination Survey (NHANES) data. We hypothesized that acrolein metabolites were positively associated with diabetes and insulin resistance.

2. Methods

2.1. Study population

The 2005–2006 NHANES, conducted by the U.S. National Center for Health Statistics (NCHS; Centers for Disease Control and Prevention, Atlanta, GA) is a cross-sectional, nationally representative survey of the non-institutionalized civilian population of the United States (Johnson et al., 2013). The survey employs a multistage stratified probability sample based on selected counties, blocks, households, and individuals within households. Certain subgroups of the population, such as Mexican American individuals, black non-Hispanic individuals, and older adults were oversampled to improve the estimate precision for these groups. The NCHS Research Ethics Review Board approved the NHANES 2005–2006 study protocols and all participants provided written informed consent. For our analysis, the study population is limited to individuals who were aged 20 years or older from whom urinary acrolein metabolites 3-HPMA and CEMA measurements were available. Pregnant women (n=147), women who were breastfeeding (n=23), and participants missing other co-variables of interest were excluded leaving a total of 2027 eligible participants.

2.2. Exposure measurements

The concentrations of the urinary acrolein metabolites—3-HPMA and CEMA—were determined using ultra performance liquid chromatography coupled with electro spray tandem mass spectrometry (UPLC-ESI/MSMS) (Alwis et al., 2012), by the Division of Laboratory Sciences (DLS), National Center for Environmental Health (NCEH), CDC. Levels below the limit of detection were entered as the limit of detection divided by the square root of two (Johnson et al., 2013). Moreover, an internal acrolein dose variable (∑Acrolein) was created based on the sum of the molar 3-HPMA and CEMA. Urinary 3-HPMA and CEMA and ∑Acrolein were categorized as weighted quartiles based on the distribution of the urinary acrolein metabolite levels among the study population.

3. Outcome of interest

3.1. Diabetes case definition

Diabetes was defined as glycated hemoglobin (A1C) ≥ 6.5% or fasting plasma glucose (FPG) ≥ 126 mg/dl, or self-reported current use of insulin or diabetes medication.

Information on participants' current use of insulin and/or oral anti-diabetes medications were obtained during the household interview. Glycated hemoglobin was measured using ion exchange chromatography. Fasting plasma glucose was measured using the hexokinase enzymatic method.

3.2. Insulin resistance and HOMA, HOMA-B, fasting insulin, and fasting plasma glucose

Markers of diabetes risk were determined in a subsample of 850 individuals not taking insulin or medication for diabetes. Insulin resistance was assessed using HOMA-IR (homeostatic model assessment). HOMA-IR is epidemiologically practical, widely used, and correlates acceptably (R=0.73–0.88) with the hyperinsulinemic-euglycemic clamp test, which is generally considered to be the gold standard (Matthews et al., 1985; Wallace et al., 2004). HOMA-IR was calculated as fasting plasma glucose (mmol/L) x fasting insulin (uU, mL)/22.5 and insulin resistance was defined as HOMA-IR > 2.6 (Ascaso et al., 2003, Loprinzi and Abbott, 2014; Velagaleti et al., 2010; Zhao et al., 2014). Although our primary study outcome was insulin resistance, we also examined continuous HOMA-IR, beta-cell function (HOMA-β), fasting insulin, and fasting plasma glucose in secondary analyses. HOMA-β was calculated based on the formula: HOMA-β=[(20*fasting insulin)/(fasting plasma glucose – 3.5)] (Matthews et al., 1985).

3.3. Statistical methods

To account for the complex, multistage sampling design of NHANES, we performed all analyses using the appropriate sample weights, strata, and cluster variables. All analyses were performed using the weights from the volatile organic compounds metabolites subsample as recommended by NCHS (Johnson et al., 2013.). SAS 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses and SAS-Callable SUDAAN 10 (Research Triangle Institute, Research Triangle Park, NC) was used to account for the NHANES complex sample design. P-values were presented at the significance level of 0.05. Multivariable logistic regression was used to calculate adjusted odds ratios (ORs) for diabetes and insulin resistance (HOMA-IR > 2.6) by comparing participants in the highest urinary acrolein metabolites compared to their referent lowest quartile.

We ran three models: model 1 was adjusted for urinary creatinine and age; model 2 was further adjusted for demographic and socio behavioral variables, such as sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and Other), education (less than high-school, high school graduate, some college, and above), alcohol consumption self-reported smoking status (current, former, or never smoker), serum cotinine (a biomarker of exposure to environmental tobacco smoke was natural log-transformed) and fasting time; and model 3 was further adjusted for confounding factors such as body weight status (underweight/normal, overweight and obese), and moderate and vigorous recreational activities.

To account for variation in the dilution of spot urinary samples, urinary creatinine was entered into the models as an independent variable, as suggested by previous studies (Barr et al., 2005). Serum cotinine was measured by an isotope-dilution-high-performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry method (Bernert et al., 1997). Information about age (years), sex, race/ethnicity, and education were obtained from the household interview. Age was categorized as quartiles based on the weighted distribution of age among the study population. Race/ethnicity was divided into four categories: non-Hispanic White, non-Hispanic Black, Mexican American and Other (Other Hispanic and other race). Body weight status was classified as normal/underweight, overweight, and obese with body mass index (BMI) measures of < 25, 25– < 30, and ≥ 30, respectively. Alcohol consumption and self-reported smoking status (current smoker, former smoker, or never a smoker) were obtained from the physical examination and associated questionnaire. Participants that reported smoking at least 100